VOLUME 79 • MARCH 1959 • NUMBER 3

A.M.A. ARCHIVES OF

DERMATOLOGY

The Treatment of Dermatomycoses with Orally Administered Griseofulvin
Harvey Blank and Frank J. Roth Jr.

Some Practical Aspects of the Diagnosis and Management of Shoe Dermatitis
A. A. Fisher

A Contrast of Cutaneous Cancer as Observed in Texas and in Minnesota
Francis W. Lynch, C. Ferd Lehmann, and J. Lewis Pipkin

The Comparative Effect of Various Wet Dressings upon Aseptic Cutaneous-Wound Healing in Man
Ray O. Noojin, Robert A. Lewis, and Charles H. Lupton

Subcutaneous Filarial Infections
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Triamcinolone in the Treatment of Psoriasis
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Edward H. Mandel

Spring Supports for the Drive Shaft of Planing Machines
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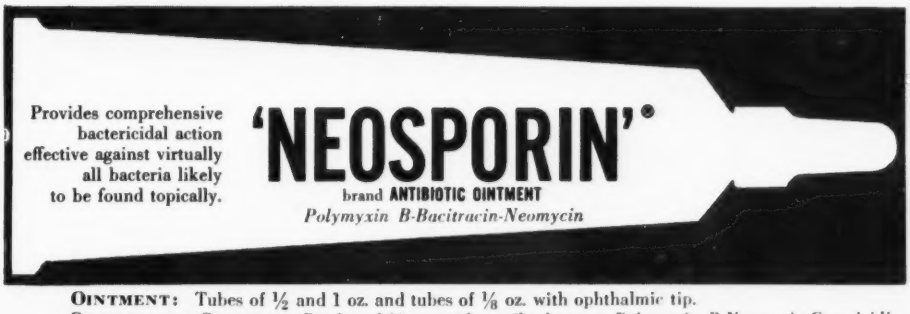
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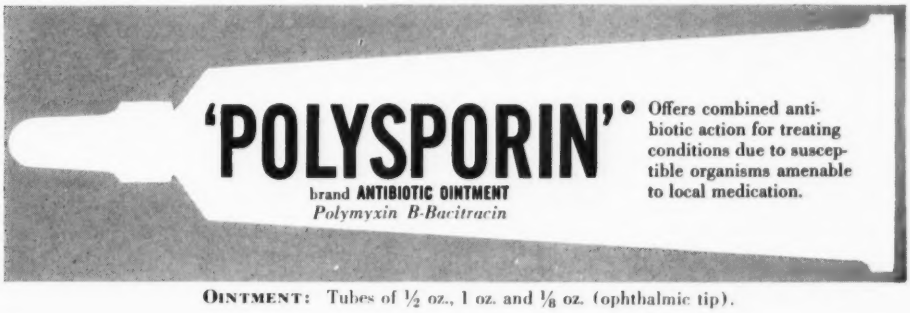
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Bibliography:

1. *Hollander, J. L.; Brown, E. M., Jr.: Jessar, R. A.; Smukler, N. M.; Udell, L.; Stevenson, C. R., and Bowie, M. A.: Paper read before Interim Session, American Rheumatism Association, Bethesda, Maryland, Dec. 6, 1957.*
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References: 1. Sokoloff, O. J.: Meprobamate (Miltown) as adjunct in treatment of anogenital pruritus. A.M.A. Arch. Dermat. **74**:393, Oct. 1956. 2. LeVan, P.: Clinical dermatologic studies of four chemically different tranquilizers. Clinical Med. **4**:1089, Sept. 1957.

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References: 1. Gaillard, G. E.: J. Allergy 21:55, 1950
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3. Passenger, R. E., Spain, W. C. and Strauss, M. B.: J. Allergy 27:409-423, 1956
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5. Fontana, V. J.: GP 10:47, 1954
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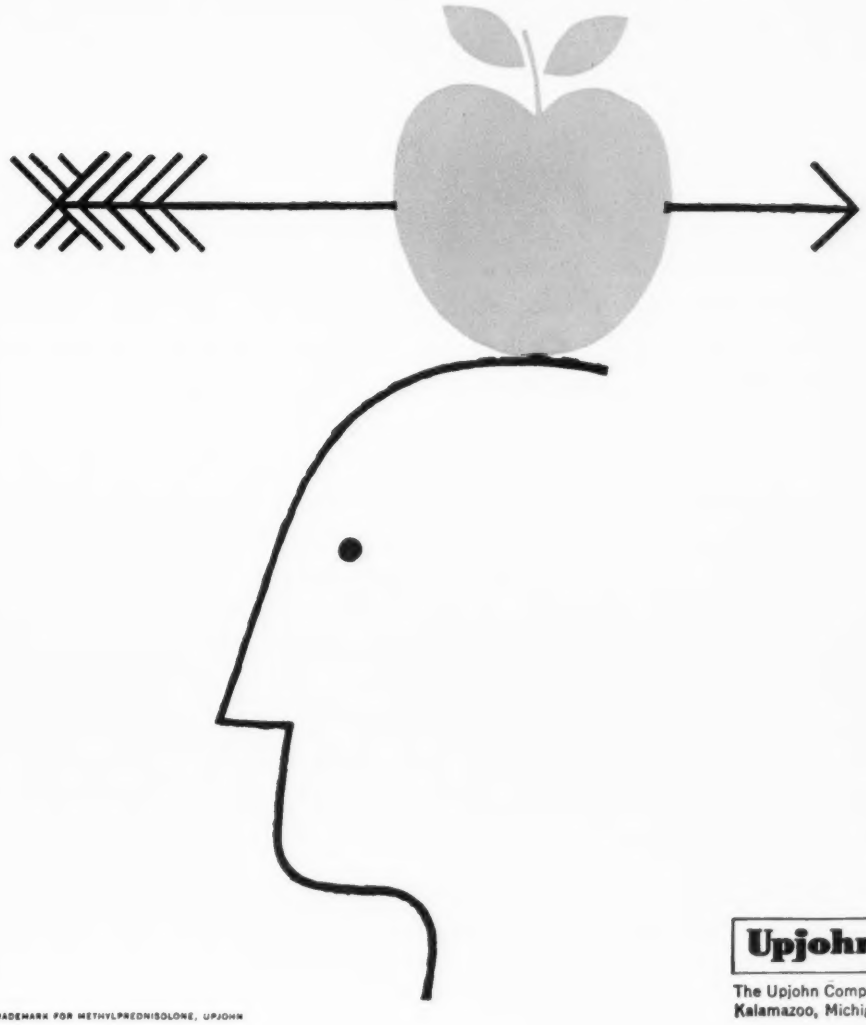

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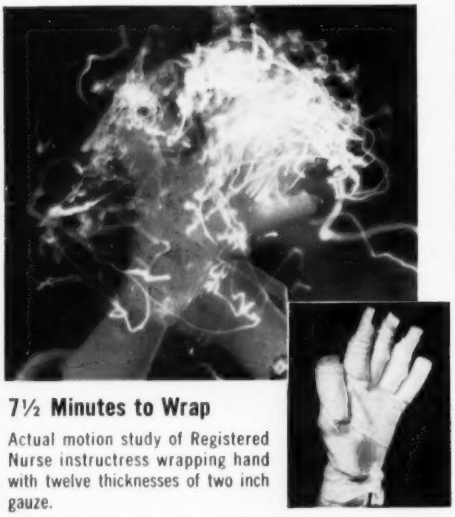
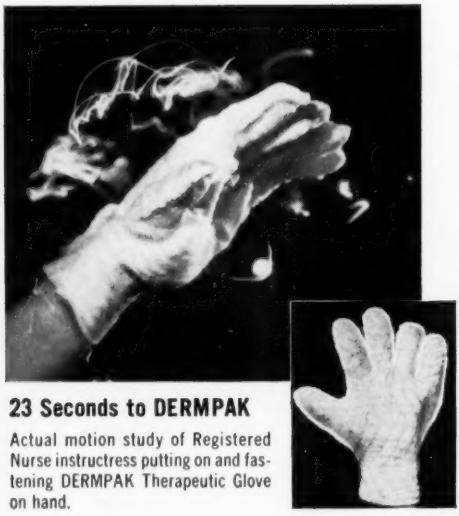


7½ Minutes to Wrap

Actual motion study of Registered Nurse instructress wrapping hand with twelve thicknesses of two inch gauze.



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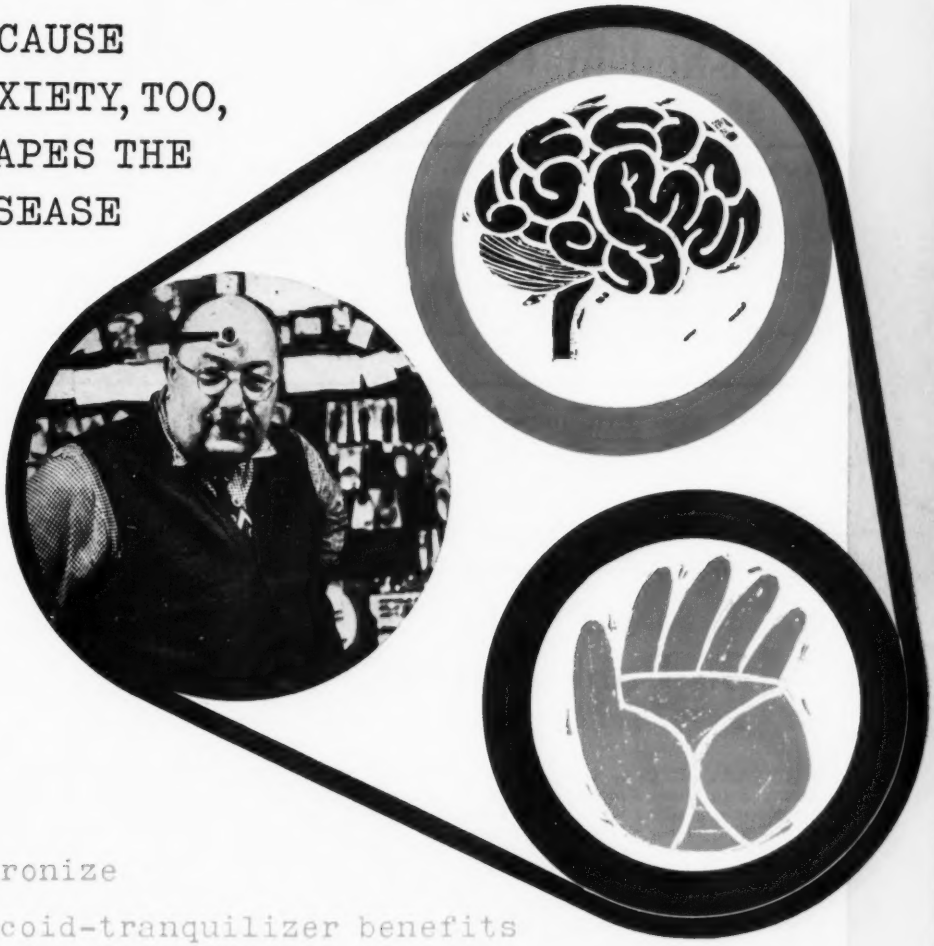

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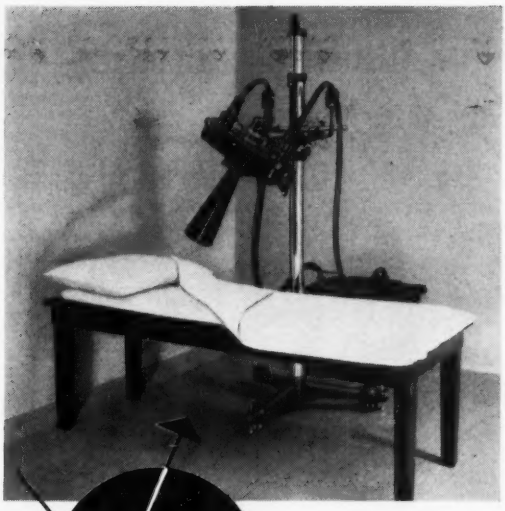

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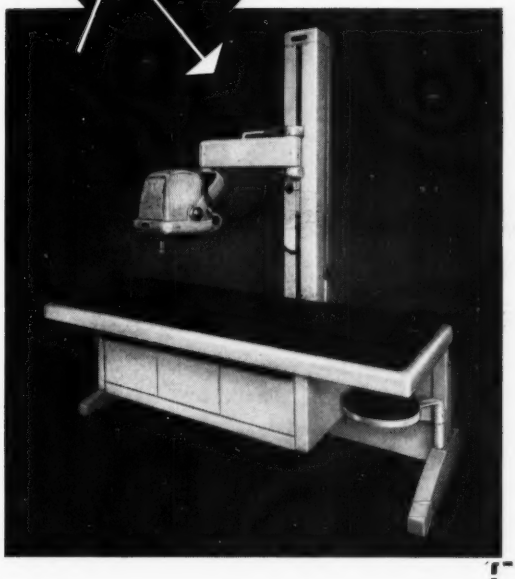

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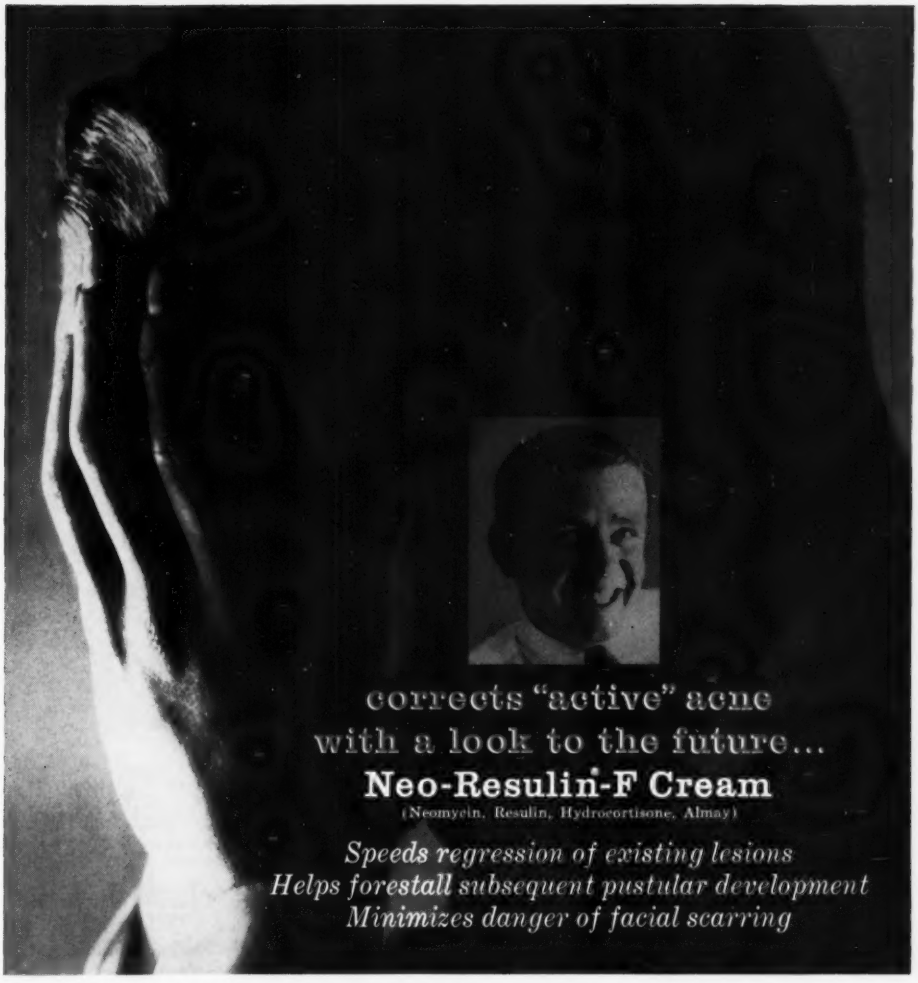
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(1) Miller, E. W., Jr.: New York J. Med. *56*:1446, 1956.

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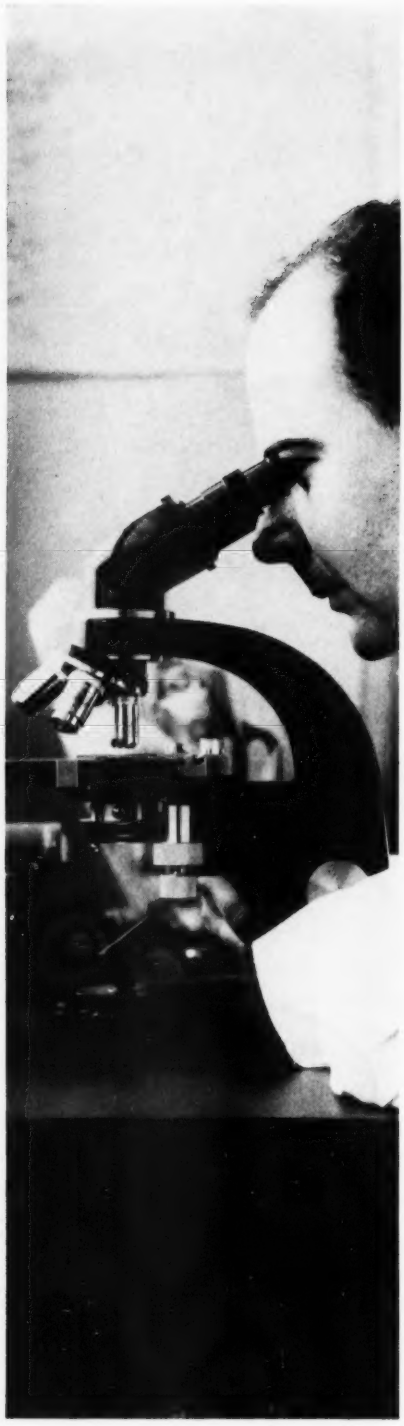

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1. Lehman, A. J.: J.A.M.A. *164*:416 (May 25) 1957.

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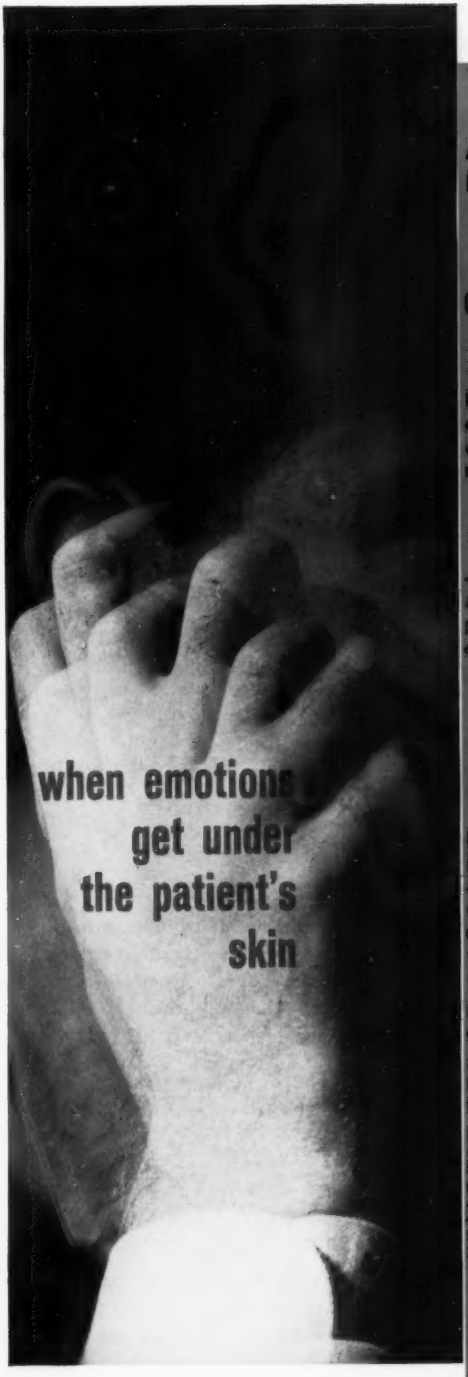

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References: 1. Feinberg, A. R., et al.: J. Allergy 29:358 (July) 1958. 2. Robinson, H. M., Jr., et al.: South. M. J. 50:1282 (Oct.) 1957. 3. Santos, I. M., and Unger, L.: Paper presented at 14th Annual Congress, American College of Allergists, Atlantic City, New Jersey, April 23-25, 1958. 4. Colrault, M., et al.: Presse méd. 64:2239 (Dec. 26) 1956. 5. Robinson, H. J., Jr., et al.: J.A.M.A. 161:604 (June 16) 1956.

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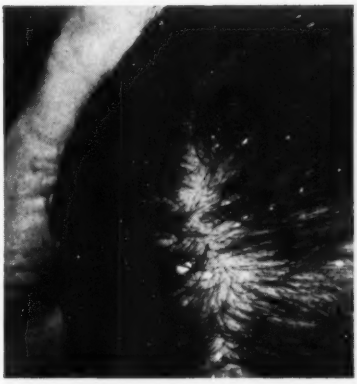

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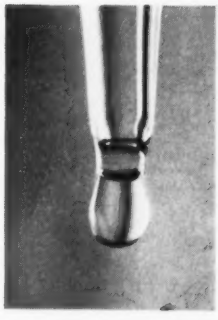

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*Zakon, S. J., et al.: Arch. Dermat. & Syph. 56:499, 1947; abstracted in Birmingham, D. J., and Campbell, P. C., Jr.: Occupational and Related Dermatoses, U. S. Public Health Service Publication No. 364, 1954.

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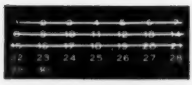

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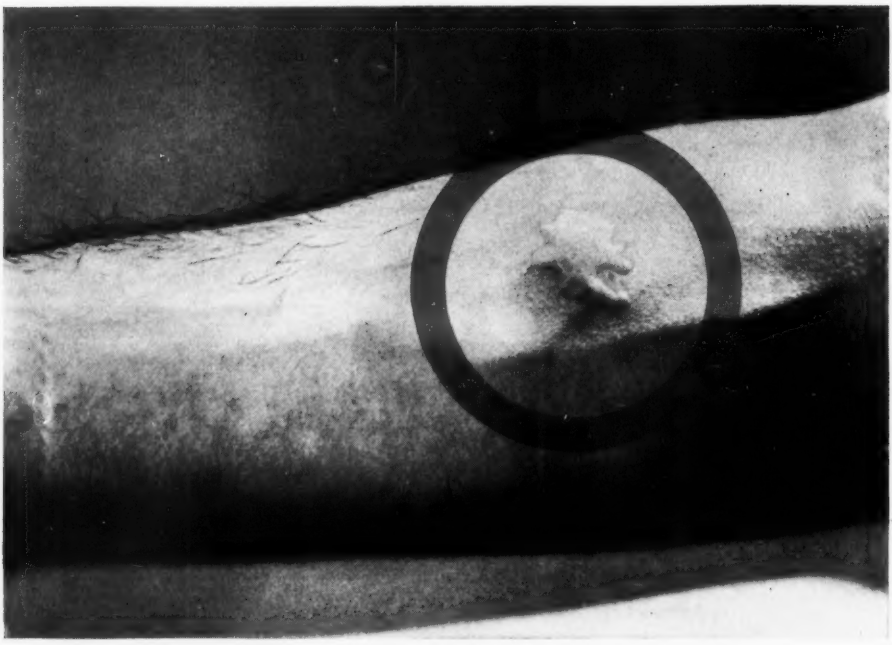

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◆ These are unretouched photographs of an actual case, infant K. M., age 3 mths.
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*Reference: Mayer, D. McC., and Swanker, W. A.: Anomalies of Infants and Children, New York, McGraw-Hill Book Co., Inc., p. 97, 1958

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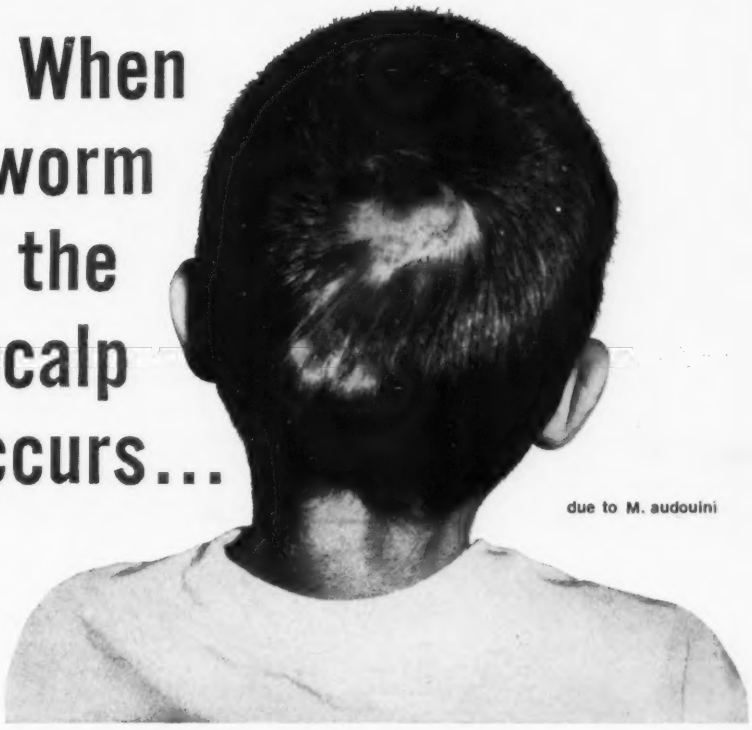

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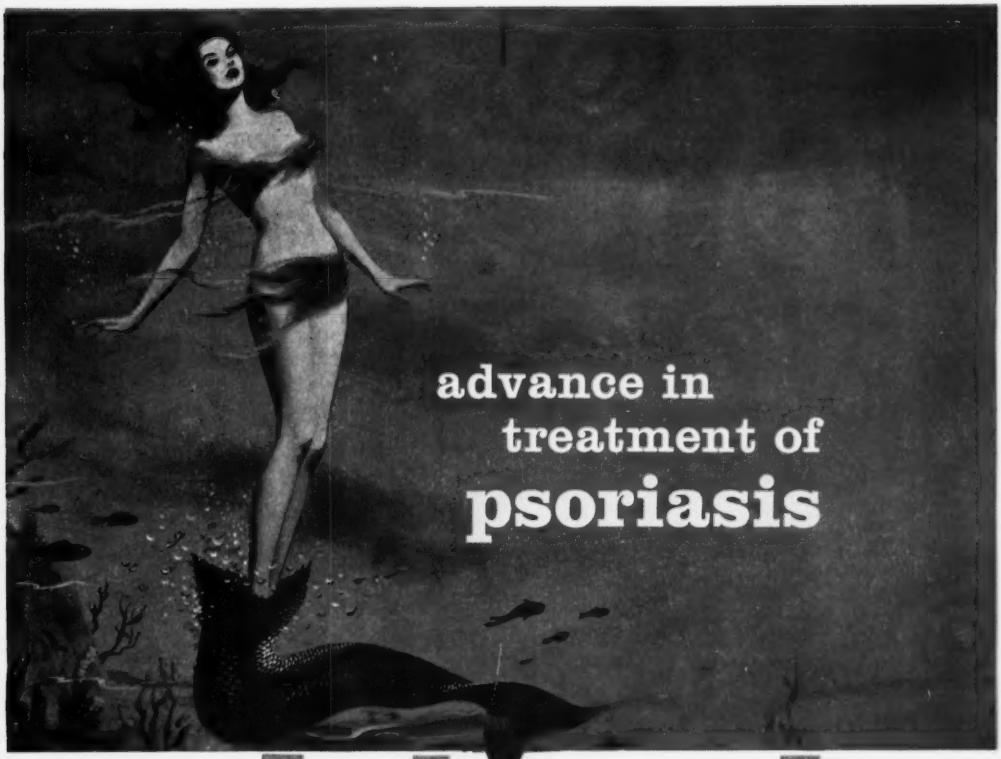

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(1) Flesch, P.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (2) Bleiberg, J., and Saltzman, J. A.: Clin. Med. 5:485 (Apr.) 1958. (3) Bleiberg, J.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (4) Clyman, S. G.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). *Trademark

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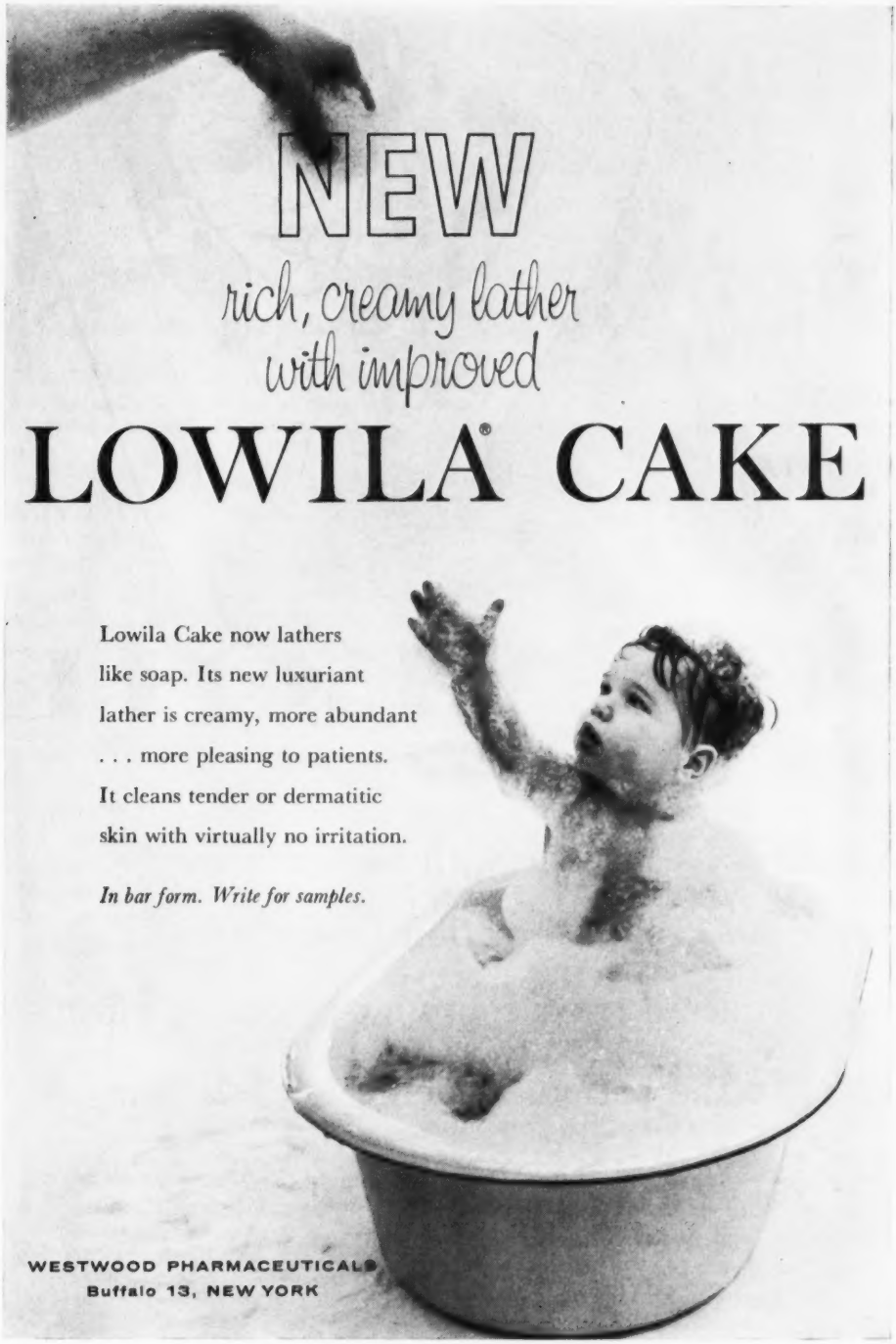
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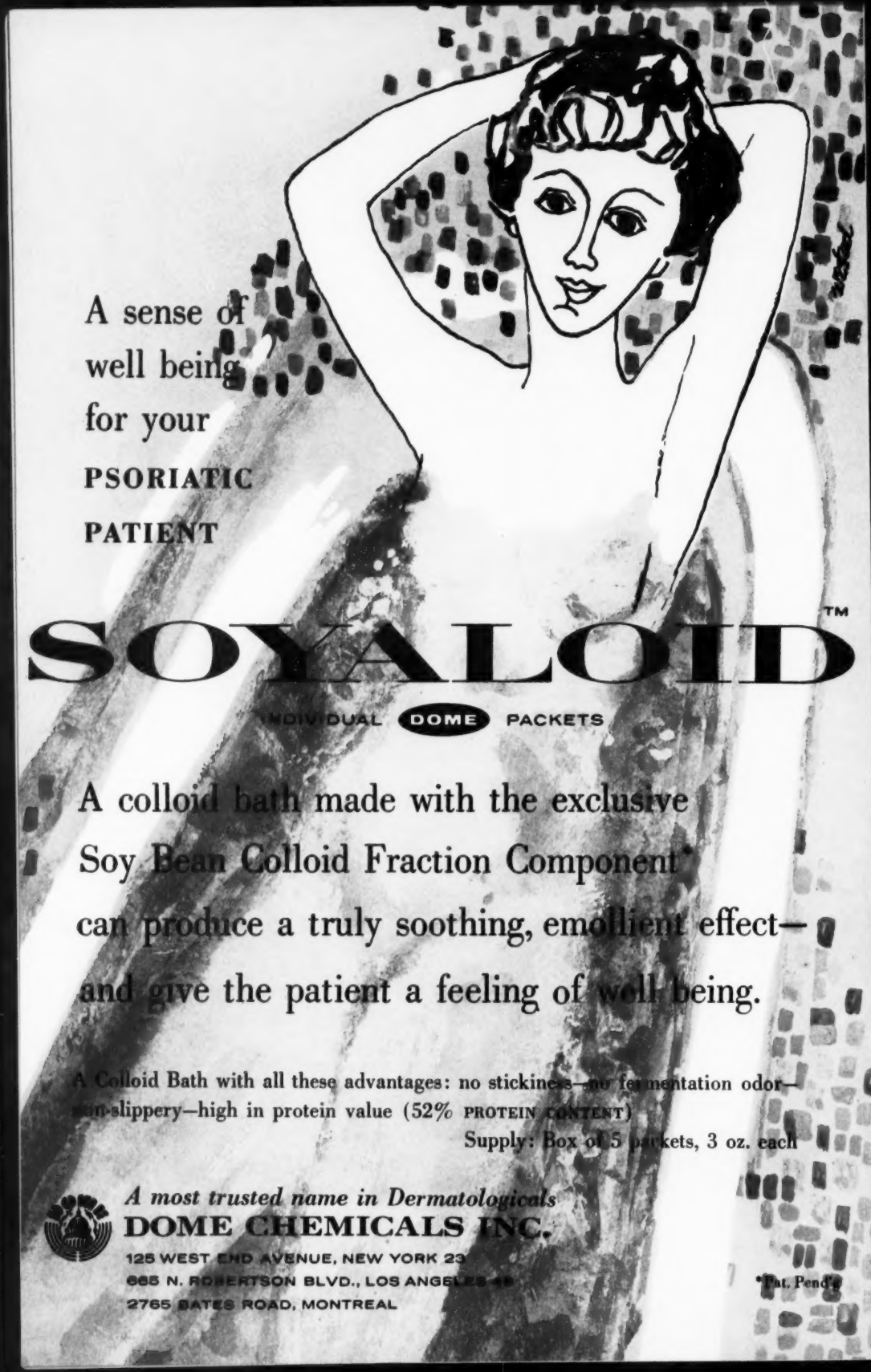
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A.M.A. ARCHIVES OF
DERMATOLOGY

The Treatment of Dermatomycoses with Orally Administered Griseofulvin

HARVEY BLANK, M.D., and FRANK J. ROTH Jr., Ph.D., Miami, Fla.
With the Assistance of William W. Bruce, M.D.; Marvin F. Engel, M.D.; J. Graham Smith Jr., M.D., and Nardo Zaias, M.D.

The systemic treatment of superficial fungus infections in man at last seems a near reality. Although the polyene antibiotics derived from streptomyces were a significant advance in antifungal chemotherapy against the yeast-like fungi, they failed to influence the common dermatomycoses.[1] Recent studies demonstrating the influence of serum factors in superficial fungous infections illustrated the importance of blood-borne substances in confining cutaneous invasion by dermatophytes.[2,15] Gentles' recent report of the successful oral treatment of Trichophyton and Microsporum infections in guinea pigs with griseofulvin, a product of several penicillia, was a great step forward.[7] Subsequently, Lauder and O'Sullivan found it effective by mouth in calves with Trichophyton verrucosum infections.[11] Our paper is a preliminary report of observations on the effectiveness of oral griseofulvin therapy in man.

Submitted for publication Dec. 31, 1958.
Presented at the American Academy of Dermatology & Syphilology, Chicago, Dec. 6-11, 1958.

From the Division of Dermatology, Department of Medicine, University of Miami School of Medicine, Miami, Fla., and the Veterans Administration Hospital, Coral Gables, Fla.

This study was supported in part by U. S. Army Contract No. DA-49-007-MD-731 and by grants from the Hazen-Brown Fund of Research Corporation and from the National Institutes of Health, PHS No. E-1546.

Griseofulvin is a colorless, neutral, thermostable antibiotic isolated from Penicillium griseofulvin by Oxford, Raistrick, and Simonet,[13] in 1939. Interest in the substance was revived when Brian and co-workers,[4,5] in 1945-1946, isolated a "curling factor" from cultures of Penicillium janczewski, which Grove and McGowan [8] later demonstrated to be identical with griseofulvin. In a series of publications,[3,6,9,10,16] the chemical structure of the substance was established and its activity against a number of fungi reported. Griseofulvin appeared to be most useful against infections in plants, in which it also shows systemic antifungal activity and was particularly effective for botrytis infections of lettuce and alternaria blight of tomatoes.[6]

Clinical Observations

The present study was initiated, following Gentles' paper, by treating a desperate and unique case of widespread cutaneous Trichophyton rubrum granulomas (to be reported in detail elsewhere) with griseofulvin.* Studies in their laboratories suggested that the drug had a low toxicity after oral administration. On a daily dose of 5.0 gm. of griseofulvin our patient showed a prompt response, with healing of

* Supplied by Drs. H. M. Walker and A. F. Campbell, of Glaxo Laboratories, England.

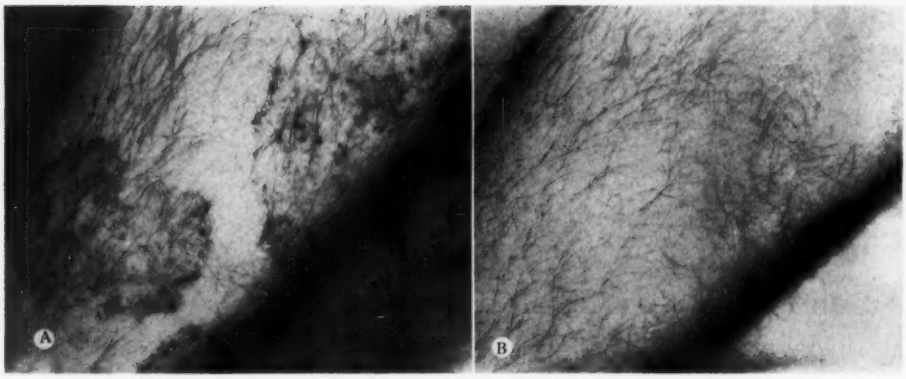

Fig. 1 (Patient 1).—T. rubrum infection of leg. *A*, before, and *B*, after three weeks of oral griseofulvin 5 gm. per day. He also had deep granulomatous lesions elsewhere.

the granulomas and subsidence of concomitant circinate tinea lesions (Fig. 1). Later it was noted that normal nail growth was replacing the distal diseased portion (Fig. 2). He failed to show any adverse clinical or laboratory signs; therefore, the drug was used in other patients under hospital supervision and eventually in outpatients. In correspondence, Dr. Gentles indicated that in recent work he had found 15 mg. per kilogram curative in guinea pigs. We subsequently reduced the dose for most patients to 2.0 gm. and later to 1.0 gm. a day, given as 250 mg. tablets four times a day.

The results of our observations on 31 patients who have been followed sufficiently long to allow for a conclusion are summarized in Table 1. In this Table, the major body areas of involvement and the etiologic agents isolated are indicated as well as the duration of the disease before griseofulvin was given. In many cases, particularly the recent ones, a single dosage level of 1.0 gm. was used; in two cases a dose of 4.0 or 5.0 gm. was given for one month and then changed as indicated. The "time to clear" column indicates clinical involution of active lesions. In most cases repeated mycologic examinations at 72-hour intervals produced negative cultures in one to two weeks or less and a negative direct KOH preparation in about two weeks. Cultures of hairs and nails remained positive until the abnormal infected material was naturally or mechanically removed. The duration of post-treat-

Fig. 2 (Patient 1).—T. rubrum infection of fingernails. *A*, after 7 weeks, *B*, after 12 weeks of oral treatment.

TABLE 1.—*Clinical Results of Oral Griseofulvin Therapy*

Patient	Age	Race	Sex	Location of Lesions	Organism	Duration of Disease, Yr.	Daily Dose, Gm.	Duration of Treatment, Wk.	Time to Clear, Wk.	Duration of Post-Treatment Follow-Up, Wk.	Comments
1	26	W	M	Granulomas	T. rubrum	4	5-2-1	15	Ca. 6		Still on treatment
				Body & extremities	T. rubrum	5	5-2-1	15	2		Still on treatment
				Nails	T. rubrum	4	5-2-1	15	15		Grown out normally
2	65	N	F	Body & face	T. rubrum	4 mo.	2	2	2	6	
				Groin	T. rubrum	4 mo.	2	2	2	6	
3	24	W	M	Buttocks & groin	T. rubrum	2	2-1	3	2	5	
				Palms	T. rubrum	2	2-1	3	2	5	
4	22	W	M	Buttocks	T. rubrum	2	2	3	2	4	Rubrum cleared, but versicolor unaffected
				Trunk	M. furfur	Unknown	2	3	Failure		
5	56	W	M	Body	T. rubrum	5	2	2	2	5	Normal nail is growing in
				Feet	T. rubrum	5	2	2	3	5	
				Nails	T. rubrum	5	2	2			
6	65	W	M	Body	T. rubrum	Unknown	2	4	3		Penicillin reaction unaffected by griseofulvin
				Groin	T. rubrum	Unknown	2	4	3		
7	24	W	M	Body & arms	T. rubrum	2	2	6	3	2	
				Feet	T. rubrum	2	2	6	4	2	
8	70	N	M	Buttocks & groin	T. rubrum	37	2	3	2	1	
9	60	W	F	Trunk	T. rubrum	12	1	2	2	6	
				Feet	T. rubrum	12	1	2	2	6	
10	71	N	F	Generalized	T. rubrum	30	1	3	3		
11	50	N	M	Feet & toenails	T. rubrum	1	1	2	2		Nails under observation
12	45	N	F	Feet	T. rubrum	5	1	4			Normal area of nails appearing
				Toenails							
13	26	W	M	Feet	T. rubrum & C. albicans	4	2	3	Worse at first		Cleared with topical nystatin; moniliasis a complication
14	43	W	M	Nails	T. rubrum	5	1.5	3		3	Nails clearing 6 wk. after begin. treatment
15	28	W	M	Feet	T. rubrum	5	1	6	6		"Moccasin" type lesion
16	30	W	M	Palms	T. rubrum	3	1	4	4	1	
17	44	W	F	Body & groin	T. rubrum	8	1	3	3	3	
18	23	W	M	Feet	T. mentagrophytes	3	1	12 da.	15 da.	1	Clearing occurred after treatment was discontinued
19	40	W	F	Feet	T. mentagrophytes	9	1	10 da.	4		Clearing occurred after treatment was discontinued
20	67	W	F	Scalp	T. tonsurans	60	2	5	4	2	Urticarial drug rash?
21	6	N	M	Scalp	M. audouini	Unknown	1-2	4	4	3	Gentle debridement

TABLE 1.—*Clinical Results of Oral Griseofulvin Therapy*—Continued

Patient	Age	Race	Sex	Location of Lesions	Organism	Duration of Disease, Yr.	Daily Dose, Gm.	Duration of Treatment, Wk.	Time to Clear, Wk.	Duration of Post-Treatment Follow-Up, Wk.	Comments
22	6	N	M	Scalp	M. audouini	1	1	4	3	1	Shaved scalp at 18 days
23	15	W	M	Trunk	M. canis	9 da.	1	1	1	4	
24	5	W	M	Trunk	M. canis	6 da.	1	1	1	4	
25	9	W	M	Scalp	M. canis	1 mo.	1	4	4	2	
26	24	W	F	Body	M. canis	4 wk.	1	2	2	4	
27	21	W	M	Groin	E. floccosum	15 mo.	1.5	14 da.	2	2	
28	45	W	M	Face	Blastomycosis	2	4-5	6	Failure		Later cleared with intravenous Amphotericin B
29	39	W	M	Body	M. furfur	5	1	4	Failure		
30	12	N	M	Face	M. furfur	4 mo.	1	3	Failure		
31	27	W	F	Body	M. furfur	2	1	3	Failure		

ment follow-up indicates the period of observation after clinical clearing and after discontinuing further therapy. The only relapse, if it can be called that, appeared in the patient with the granulomas. He developed a single peculiarly resistant 3 cm. scaling area of ringworm, with repeated positive cultures on the forearm. Nails and ringworm elsewhere have remained in complete remission during four months of continuous therapy.

Most of the patients have been carefully photographed to facilitate objective assessment of clinical improvement. The several figures illustrate characteristic types of response which have been observed.

Toxicity and Adverse Reactions

Studies of the formed elements and chemical constituents of blood, including procedures measuring liver and kidney function, urinalyses, etc., have continued to confirm our early observations that oral griseofulvin is a drug of low toxicity in man.

The adverse reactions observed include one case of a possible urticaria-like drug eruption after five weeks of continuous therapy with 2.0 gm. of griseofulvin a day, which subsided when the drug was stopped. It is of interest that several patients with a history of penicillin sensitivity failed to develop reactions to griseofulvin. One patient was given an injection of penicillin after two weeks of griseofulvin and developed urticaria, which subsided in several days even though the griseofulvin was continued. Several patients have noted mild abdominal distress and several others, headaches, which subsided with continuing administration of the drug.

During the present study it was reported that griseofulvin when given in sublethal doses intravenously or intraperitoneally to rats caused arrest of mitosis of rapidly dividing cells of the intestine, testes, and bone marrow.[12] Although such effects in animals are not seen on oral administration of doses far in excess of therapeutically effective amounts (unpublished observa-

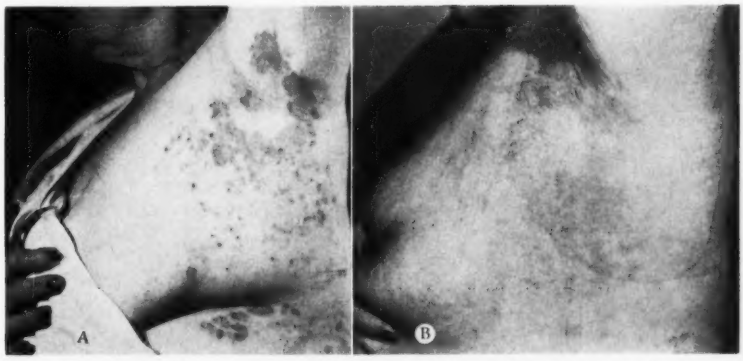

Fig. 3 (Patient 9).—T. rubrum infection of trunk of 12 years' duration. *A*, before treatment. *B*, after two weeks of oral griseofulvin, 1.0 gm. per day.

tions of Glaxo Laboratories), it was felt necessary to look for any evidence of such action in man. The more detailed results of the laboratory studies in our patients will be presented at a later time. Suffice it to say that no evidence of an antimitotic effect has been seen. One of the most significant observations was made by our consultant hematologist, Dr. Ulfar Jonsson, who performed counts of the number of mitoses in the bone marrows of five patients who were treated for extended periods with doses in excess of those which are likely to be used in future patients. These results are given in Table 2 and show no significant change in the karyokinetic index in either the white or red blood cell series.

In Vitro Observations

Preliminary studies, which will be published in greater detail elsewhere,[14] have confirmed the exquisite sensitivity to griseofulvin of the dermatophytic fungi. The following organisms are completely inhibited for 72 hours by 0.2μg.-0.4μg. of griseofulvin per milliliter: Microsporum canis, Microsporum gypseum, Microsporum audouini, Epidermophyton floccosum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton megnini, and

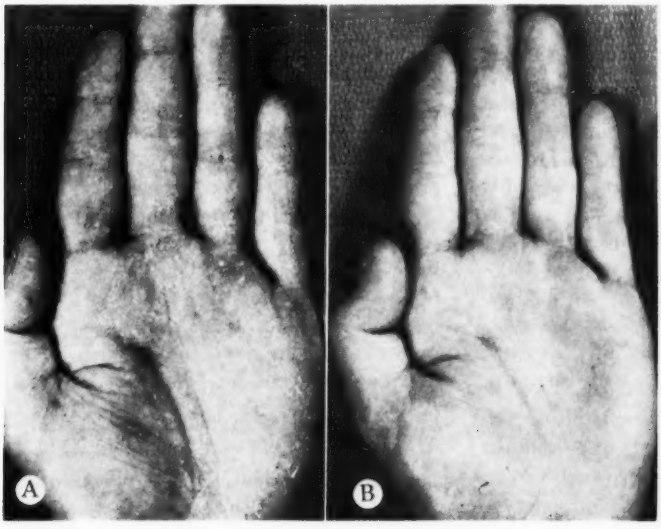

Fig. 4 (Patient 3).—T. rubrum infection of right hand of two years' duration. *A*, before treatment. *B*, after oral griseofulvin, one week of 2.0 gm. per day and one week of 1.0 gm. per day.

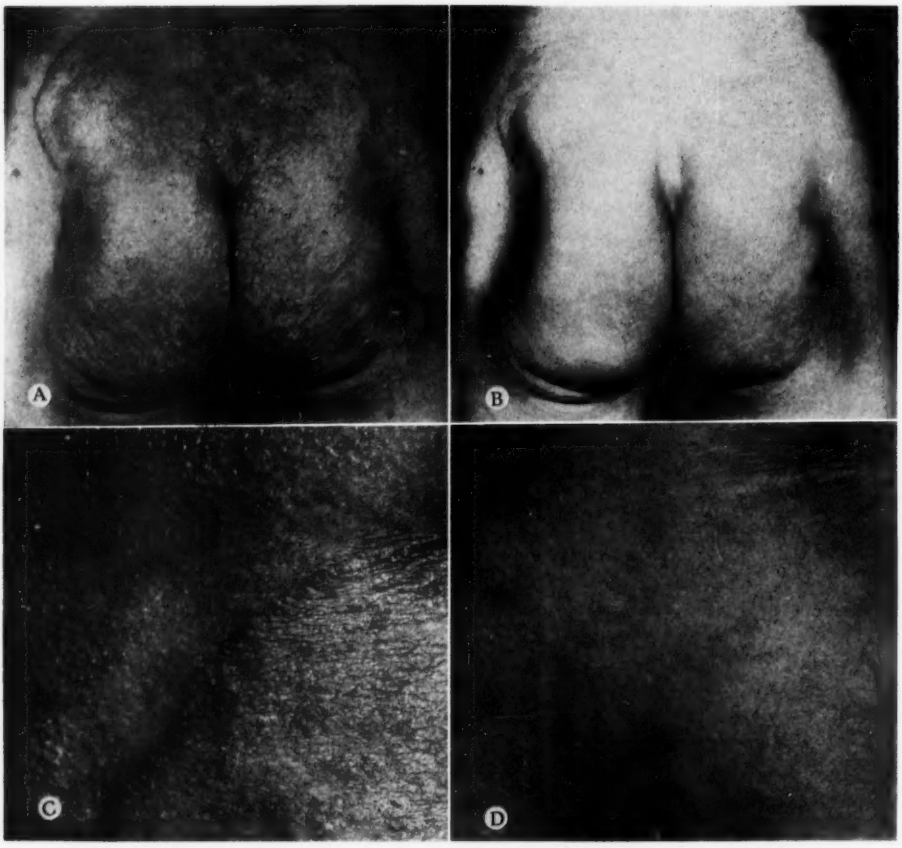

Fig. 5 (Patient 4).—T. rubrum of buttocks of two years' duration. *A* and *C*, before treatment. *C* and *D*, close-ups of the upper left border of the lesion. *B* and *D*, after two weeks of oral griseofulvin, 2.0 gm. per day.

Trichophyton gallinae. T. rubrum is most sensitive, 0.14μg.-0.18μg. per milliliter being sufficient to cause complete inhibition. It is important to note that in concentrations likely to be achieved in man, griseofulvin is fungistatic rather than fungicidal. Fungous pellets suspended in griseofulvin-containing broth for as long as 14 days and washed thoroughly produced normal colonies when plated on antibiotic-free media. The development of resistance to the drug by the dermatophytes has not been encountered. The following organisms were found insensitive to 30μg. per milliliter: Candida albicans, Cryptococcus neoformans, Sporotrichum schenkii, Hormodendron compactum, Phialophora verrucosa, Blastomyces dermatitidis, Blastomyces brasiliense, and Histoplasma capsulatum.

Direct bioassay [15] of the urine from six present for a few weeks or months.
of more than 50% of orally administered griseofulvin. A similar assay of serum known to contain the drug, however, failed to demonstrate antibiotic activity. These results indicate that some type of extraction procedure is required for accurate determinations of blood levels.

Summary and Provisional Conclusions

Mycoses caused by various species of dermatophytes show a uniformly favorable response to oral therapy with griseofulvin.

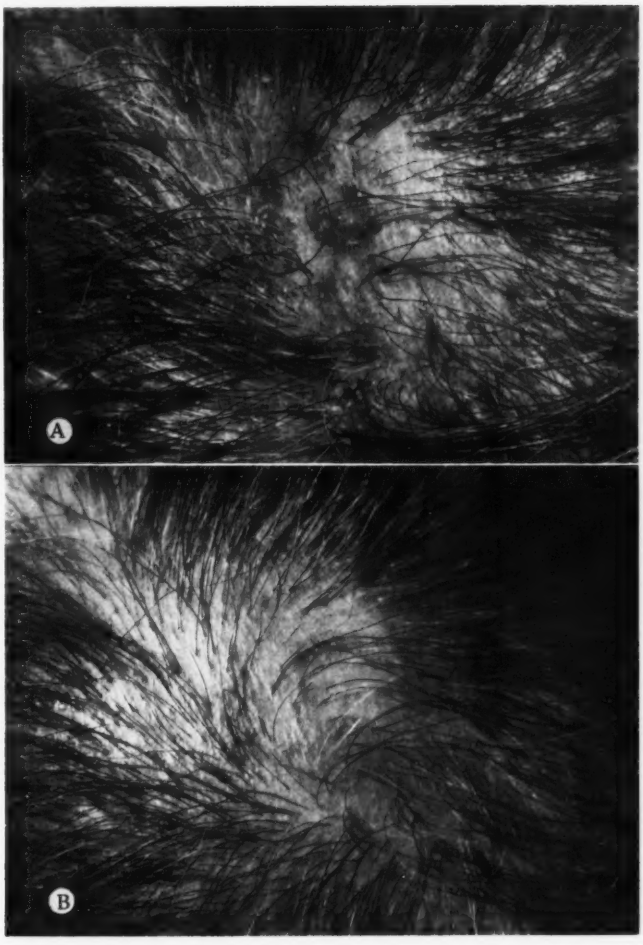

Fig. 6 (Patient 20).—T. tonsurans of the scalp of 60 years' duration. *A*, before treatment, showing multiple inflammatory papules with infected "black dots" of hair stubs and scaling. *B*, after five weeks of oral griseofulvin, 2 gm. per day, the process has cleared, and a number of new growing short hairs can be seen. The two black dots remaining contained only noninfectious debris.

TABLE 2.—*Bone Marrow-Karyokinetic Indices* *

	Patient	Pretreat. Level, %	Repeat Exam., %	Duration of Treat. at Time of Repeat, Days	Dosage, Gm/Day
1	Wbc	0.6	1.0	74	5-1
	Rbc	1.3	1.0		
2	Wbc	0.3	0.6	37	4-5
	Rbc	1.6	1.3		
3	Wbc	—	0.3	18	2
	Rbc	—	2.0		
4	Wbc	—	0.3	22	2
	Rbc	—	2.3		
5	Wbc	—	0	30	2
	Rbc	—	1.3		

* Normal range: Wbc series, 0.1%-1%; Rbc series, 1.0%-4.6%.

Infections of long duration, up to 60 years, seem to respond as readily as those patients indicated excretion by this route

Infections caused by Candida albicans, Malassezia furfur, and Blastomycosis dermatitidis do not seem to respond to this therapy.

Tinea corporis is usually cleared in one to two weeks; itching usually ceases in three to five days.

Tinea pedis is improved in one to two weeks but may require three to four weeks or longer to clear.

Tinea capitis improves in two to three weeks but may require more prolonged treatment.

Onychomycosis requires three to four months to clear, but new normal nail growth is seen earlier. The optimum duration of therapy is not known.

Cultures of epithelial lesions often become negative in one week. Direct KOH examinations may be positive for an additional week or more.

Infected nails and hair appear to contain viable fungi until the involved portions are replaced by healthy new growth.

Although toxic reactions appear to be minimal in therapeutic doses in man, the animal data indicate that repeated peripheral blood cell counts at least should be performed during a course of prolonged therapy.

One patient developed an urticaria-like drug eruption after six weeks of continuous therapy, and others have had mild self-limited complaints of gastrointestinal distress and headache.

A daily dose of 1.0 gm. seems to be adequate, although the minimum effective dose and the optimum dose have not been established for all types of infection.

The duration of treatment required probably will vary, apparently depending on the time required for normal replacement of the infected tissues.

Likelihood of relapse or recurrence of infection is as yet not known.

Drs. John Hicks and Meyer Yanowitz supplied data on several patients in the series; Dr. Burton F. Barney referred Patient 1 to us; Mr. William Atkinson and his staff did the photographic work, and Dr. G. Hildick-Smith, of Johnson & Johnson, provided recent supplies of griseofulvin (Grifulvin).

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Some Practical Aspects of the Diagnosis and Management of Shoe Dermatitis

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The diagnosis of shoe dermatitis depends on the history, the clinical picture, positive patch-test reactions to shoe material, and the patient's ability to wear proper substitute shoes without dermatitis. The management of a case of shoe dermatitis does not end with the diagnosis and the treatment of an existing dermatitis. The patient must be informed how he can obtain acceptable shoes which are free from the specific materials to which he is sensitive, since, otherwise, the patient is doomed to frequent recurrences of the dermatitis or to the wearing of such poor substitutes as canvas shoes.

In this paper I am presenting the materials for "screening" patch-tests in patients with suspected shoe dermatitis and the names and addresses of shoe manufacturers and dealers where patients may obtain shoes which are free from certain specific sensitizers.

We have found that the use of the "screening" patch-testing tray has facilitated the diagnosis of allergic contact dermatitis due to materials in shoes. It has often obviated the need for the time-consuming and tedious dissection of shoes to obtain materials for patch-testing. However, where the clinical picture strongly suggests shoe dermatitis and the patient does not react to any of the materials in the "screening" tray, it may be necessary to patch-test with the actual materials in the suspected shoe.

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Skin and Cancer Unit of the New York University Hospital.

The materials which we have used for a "screening" patch-testing shoe tray are as follows.

1. Rubber thermoplastic box-toe material. The Shoe Factory Buyer's Guide, published by Shoe Trades Publishing Company, 683 Atlantic Ave., Boston, lists under "Thermoplastic Material" the companies in various communities where one can obtain this material. When writing for this material, indicate that you wish the rubber thermoplastic material which is used in box toes. Furthermore, one can obtain this material from the box toes of most inexpensive oxford shoes. The thermoplastic material is cut into 1 in. squares and moistened with a little water and applied in the usual patch-test fashion.

2. 1% monobenzyl ether of hydroquinone in petrolatum.

3. 1% 2-mercaptobenzothiazole in petrolatum.

4. 1% tetramethylthiuram monosulfide in petrolatum.

5. 0.25% potassium dichromate in aqueous solution.

6. 2% paraphenylenediamine in petrolatum.

7. 5% nickel sulfate in aqueous solution.

The 1% monobenzyl ether of hydroquinone and the 2-mercaptobenzothiazole may be obtained from the Eastman Organic Chemicals Department, Distillation Products Industries, Division of Eastman Kodak Company, Rochester 3, N. Y. These materials should be triturated to a very fine powder and gradually added to the petrolatum. The tetramethylthiuram monosulfide, the potassium dichromate, the paraphenylenediamine, and nickel sulfate may be obtained from the Fisher Scientific Company, 633 Greenwich St., New York. The tetramethylthiuram monosulfide is prepared like the monobenzyl ether of hydroquinone and the mercaptobenzothiazole. The potassium dichromate and the nickel sulfate crystals readily dissolve in water. The paraphenylenediamine is triturated to a fine

powder and gradually added to the petrolatum.

The rubber thermoplastic box-toe material, which is listed first above, is the box toe found in most of the less expensive oxford types of men's, women's, and children's shoes. The basic material in this box toe is composed of scrap rubber, such as old tires and girdles. To the rubber is added felt, turpentine resin, rosin, styrene, asphalt, and Carbowax. To this complex are added rubber antioxidants and accelerators, and the mixture is heated to 360 F. The finished thermoplastic rubber box toe has the advantage of being inexpensive. However, it is brittle, adheres poorly, and has a low softening point, so that it will soften in very hot weather and cannot be used in the tropics.

We have been able to confirm Shatin and Reisch's [1] conclusion that the rubber thermoplastic box-toe material is one of the commonest causes of shoe dermatitis and that the rubber portion is the main sensitizer. However, it must be emphasized that a negative patch-test reaction to this material does not necessarily exonerate it from being the cause of a shoe dermatitis, since the friction, the maceration, and the leaching effect of sweat in actual use are not duplicated in the standard patch test. A dermatitis beginning on the dorsum of the toes, especially the first toe, in a patient who has worn an oxford type shoe with a firm box toe, should be considered as being caused by the rubber in the box toe unless proved otherwise.

More than one-half of our patients who showed positive patch-test reactions to the rubber thermoplastic box toe also reacted to one or more rubber "additives," such as the antioxidant, monobenzyl ether of hydroquinone, or accelerators, such as 2-mercaptobenzothiazole or tetramethylthiuram monosulfide. The significance of these findings will be discussed later when we analyze the role of rubber additives in shoe dermatitis.

After it has been established that the rubber thermoplastic box toe is the cause of the dermatitis, the patient should be instructed how to obtain shoes with box toes which do not contain rubber. One of such readily available and satisfactory box toes is that composed of Celastic material. The Celastic box toe consists of cotton flannel impregnated with pyroxylin. Pyroxylin is a cellulose nitrate. Much of this cellulose nitrate is obtained from discarded eye-glass frames. An inorganic fire retardant, a mold retardant, and a special solvent are the added ingredients of the Celastic box toe.

The solvent, the composition of which is a trade secret, "activates" the pyroxylin and cements the lining and leather completely, making a single unit in the box of the shoe. Thus, no rubber cement is used in the Celastic box toe.

The material in the Celastic box toe has not been shown to have caused sensitization of the skin, is not friable, has excellent adherence, withstands high temperatures, and retains its shape even in the tropics. However, it is more expensive than the rubber thermoplastic material.

Celastic box toe is manufactured by Celastic Corporation, 626 Schuyler Ave., Arlington, N. J., and is distributed by the United Shoe Machinery Company, 140 Federal St., Boston.

Some of the retail stores where shoes with Celastic box toe may be obtained are listed. The patient should be given a letter stating that shoes with Celastic box toe are required. Such a letter should be given to the manager of the store, rather than a salesman, who may not be familiar with the structure of the shoes for sale.

	Retailer
Men's	Johnson & Murphy
	French, Shriner & Urner
	Stacy-Adams
Women's	I. Miller
	Newton, Elkin
	Pandore
Children's	Gerberich-Payne (Boys)
	Little Yankee

If the retail shops listed are not accessible, such shoes may be obtained from Tru-Form Shoe, 5550 Broadway, New York 63, which will ship anywhere shoes that do not

contain rubber thermoplastic box toes. These shoes do not necessarily contain the specific Celastic box toes but have a similar box toe made of flannel and impregnated with pyroxylin and have proved to be satisfactory in our patients with shoe dermatitis due to rubber thermoplastic box toes.

Manufacturers of shoes, some of which contain box toes either made of Celastic material or similar box toes which *do not* contain rubber thermoplastic material are listed. On request these manufacturers will inform physicians where such shoes may be obtained.

Children's Shoes with Celastic Box Toe
Walk-In Shoe Co.,
Parkway & Columbia Sts.,
Schuylkill Haven, Pa.
(Throughout U. S. A., Alaska, Cuba, Hawaii)

Women's Shoes with Celastic Box Toe
Miller Shoe Co.,
4015 Cherry St.,
Cincinnati 23.
(Caution: Used only in certain styles; some styles contain thermoplastic rubber materials. Specify Celastic box toe. Some shoes contain box toes of cellophane and cloth which, like Celastic, are satisfactory substitutes for rubber thermoplastic box toes.)

Men's Shoes Without Thermoplastic Box Toe
Brockton Boot & Shoe Co.,
233 Clinton St.,
Brockton 69, Mass.
(Use pyroxylin or polyethylene box toe occasionally which are satisfactory substitutes. Specify shoes without thermoplastic rubber box toe.)

It should be pointed out that many patients with rubber-box-toe sensitivity may obtain relief by wearing soft-toed shoes, or shoes with uppers made of canvas, various cloths, plastics, and nylon mesh, especially if such shoes are unlined. The linings of many shoes are bound with rubber cement. The rubber cement and the rubber thermoplastic box-toe materials may have certain sensitizers in common.

Role of Rubber Sensitivity in Shoe Dermatitis

Even leather shoes contain rubber, both in the thermoplastic box toe and in the form of various rubber adhesives. Gaul and Underwood[2] indicated that adhesive materials in shoes were one of the primary causes of allergic contact dermatitis. Blank and Miller[3] emphasized that the most frequently observed allergen of shoe dermatitis was an antioxidant, such as monobenzyl ether of hydroquinone, or an accelerator, such as 2-mercaptobenzothiazole, used in rubber adhesives in the shoes. Gaul[4] showed that routine patch testing with rubber chemicals (antioxidants and accelerators) is an accurate method for detecting rubber sensitivity and that most of the positive tests were found in patients suffering with a dermatitis of the hands and/or feet.

As we have indicated previously, more than one-half of our patients with shoe dermatitis due to rubber thermoplastic box toes showed a positive reaction to one or more rubber additives. Our screening shoe tray contains the antioxidant, monobenzyl ether of hydroquinone, and two accelerators, mercaptobenzothiazole and tetramethylthiuram monosulfide. Although there are a great many other rubber additives in actual use, we have been able to confirm the impression of Blank and Miller that these three rubber compounds, which we have employed in our "screening tray," are, at present, the commonest causes of shoe dermatitis due to rubber, whether in thermoplastic box toes or in the rubber cement.

We have recently made the observation that many of our patients with shoe dermatitis were also allergic to adhesive tape. Sidi and Hincky[5] have shown that resins, turpentine, and rubber are the commonest causes of allergic adhesive-tape sensitivity. The conventional adhesive tape is "rubberized" and contains various antioxidants and accelerators which have been added to the rubber. In practically all our cases of shoe dermatitis due to rubber which had coincident adhesive-tape dermatitis there was allergic sensitivity to one or more rubber additives.

In one patient with dermatitis of the heel due to rubber cement in the heel pad, the

use of Le Page fish glue as a substitute adhesive proved satisfactory. In shoe dermatitis due to a rubber midsole, use of felt inner soles to prevent contact with the soles of the feet has prevented further dermatitis. In the anterior portion on the dorsum of the foot the Celastic box toe will prevent rubber dermatitis. The rare dermatitis on the instep due to rubber-cement sensitivity can be cured by wearing unlined moccasins or unlined cloth or plastic shoes.

We agree with Shatin and Reisch that, while rubber cements are found in various parts of the shoes, in actual practice these are not nearly as important as is the rubber in the thermoplastic box toe in causing dermatitis.

In the management of chronic or lichenified shoe dermatitis, the wearing of "nonallergic" shoes alone and the use of bland medication will not necessarily cure the dermatitis. Friction, sweating, and the habit of scratching may prolong the dermatitis. Frequently a superimposed "neurodermatitis" has to be treated. Treatment with tar and/or roentgen rays may be necessary to clear the shoe dermatitis.

Role of Chromates in Leather-Shoe Dermatitis

It will be noted that the fifth item in our "screening" tray is 0.25% potassium dichromate. The relationship of hexavalent dichromate sensitivity to shoe dermatitis is somewhat controversial. Walsh[6] pointed out that, while trivalent chromic sulfate, and in some processes hexavalent sodium dichromate, is the material *initially* used for tanning, the leather *finally* contains about 4% to 7% chromium as chromic oxide, a trivalent compound. Theoretically, when tanning is completed, all the chromium is in this trivalent form in close chemical combination with the hide protein. Until recently it was felt that the trivalent chromium was practically never sensitizing. Walsh[6] said that several dermatologists of wide experience in industrial dermatology and cutaneous allergy stated that they knew of no report or instance of reaction to trivalent chromium. Walsh tested three patients who had positive patch tests to very weak solutions of dichromate, (1:10,000 and 1:20,000). These patients showed no reactions to solutions of trivalent salts or to metallic chromium. Walsh further stated that three-fourths of all shoes are made with chrome-tanned leather containing 3% to 6% trivalent chromium. The wearing of shoes made from this leather is, in effect, a mass patch test to trivalent chromium, yet no instance of sensitization to trivalent chromium has ever been reported. These facts give a substantial basis for the assumption that sensitization to trivalent chromium does not occur. Recently, however, Morris,[7] has obtained positive patch tests to a trivalent basic chromium sulfate. We have prepared trivalent basic chromium sulfate according to Morris's method: "To a 0.2% solution of chromium sulfate, add a pinch of sodium bicarbonate to render alkaline and permit to stand and age for a week. With this solution we have obtained a single positive reaction in a series of twenty patients who were sensitive to potassium dichromate." Furthermore, Morris stated that a trivalent chromium compound can be leached from leather by the lactate portion of human sweat and forms a very complex lactatobasic chromic sulfate compound. It is conceivable that this particular compound * may on further study be found to be the actual sensitizer in shoe dermatitis due to chromates.

In our own material, we found that 18 of 68 (26%) dichromate-sensitive persons had shoe dermatitis. As Walsh pointed out, it is difficult to explain the frequent coexistence of dermatitis from shoe leather and hypersensitivity to hexavalent chromate usually used for patch testing if hexavalent chromate is not present in the final stage of leather tanning. According to Walsh there are several possible explanations:

* Dr. George Morris recently provided a supply of the lactatobasic chromic sulfate. We are now testing with both the simple basic chromic compound and complex lactatobasic chromic sulfate material.

There may occasionally be small amounts of residual hexavalent chromate that was not reduced during the "two bath" tanning process. Some of the trivalent chromium may be oxidized to hexavalent chromate during some subsequent processing of the leather. Hexavalent chromate may be used in the dyeing of some leather. Finally, there may be some peculiar relationship between shoe-leather dermatitis and positive reactions to chromate patch tests, such has been found in cement eczema.

At this point, we must emphasize the important role that perspiration plays in shoe dermatitis due to chromates and the practical implication of this role. Leather chemists [8,9] have shown that perspiration can remove the chrome from chrome tanned leather. These "leached" chrome salts generally migrate by capillary action toward the outer (grain) surface of the leather. Chemical analysis of chrome-tanned upper leather which has been exposed to heavy perspiration shows a definitely lower percentage of trivalent chrome oxide (Cr^{203}) than adjacent leather in the same shoe which has not been so exposed.

Further study is obviously necessary to clarify the relationship of potassium dichromate sensitivity to trivalent chrome sensitivity and shoe dermatitis. In our material, we did encounter several patients with dichromate sensitivity and dermatitis of the feet who were benefited by the wearing of vegetable-tanned shoes or nonleather substitutes.

When it is felt that a patient will benefit by the wearing of shoes which are not chrome-tanned, he should be instructed how to obtain shoes that are vegetable-tanned.

In requesting vegetable-tanned shoes it must be emphasized that the inner leather lining, if any, must also be vegetable-tanned. It has been our experience that frequently vegetable-tanned shoes have chrome-tanned linings. Such linings can be removed and be replaced with vegetable-tanned or cloth linings. A. F. Gallun and Sons Corporation, Milwaukee 1, Wis., is a manufacturer of vegetable-tanned leather for use in shoes.

The names of some manufacturers of vegetable-tanned shoes are given below. The patient should be given a letter stating that the vegetable-tanned shoes should have vegetable-tanned *linings* made of *Russet vegetable-tanned calf skin.* These manufacturers make mostly men's shoes.

Florsheim Shoe Co., Chicago
Nunn-Bush Shoe Co., Milwaukee
A. E. Nettleton Co., Syracuse, N. Y.
French, Shriner & Urner, Boston
Stacy-Adams, Brockton, Mass.
Stone-Tarlow Shoe Co., Brockton, Mass.
(Note: Have the patient request A. F. Gallun Cretan or Norwegian calf shoes with Russet calf skin linings.)

The I. Miller Shoe Company, 4015 Cherry St., Cincinnati 23, makes women's shoes, some of which have vegetable-tanned leather uppers. Shoes with vegetable-tanned linings can be made to order. These shoes are oxford style.

Women who wish to have non-chrome-tanned shoes which are dressier than an oxford style shoe may obtain nonleather shoes of various styles. The Williams Mfg. Co., Portsmouth, Ohio, makes *nonleather* women's shoes. This manufacturer, on request, will inform physicians where such shoes can be obtained in various localities.

Such nonleather shoes may have fabric, plastic (vinyl), or raffia (straw) uppers. The soles are of rubber composition, and the insole is a nonleather fiber. Examples of such shoes are a white linen pump Styles 880 and 890 and a dark nusuede imitation leather fabric, Styles 961, 971, 881, and 891.

Blooms, 311 6th Ave., New York, is the name of a retail store which will ship anywhere vegetable-tanned leather sandals made of buffalo hide from India.

Archfame Inc., 6 W. 37th St., New York, will ship anywhere men's, women's, and children's shoes which are vegetable-tanned and contain cloth linings. Children's shoes made of vegetable-tanned leather are not readily available, but the Archfame company will make such shoes to order.

Role of Dye Sensitivity in Shoe Dermatitis

The specific azo and aniline dyes used in shoes are usually a trade secret and are not readily made available to the physician for testing. While paraphenylenediamine is not actually used as a shoe dye, it often cross reacts with the type of dye used in shoes. The addition of paraphenylenediamine to our "screening" tray has proved helpful in alerting us to certain possibilities. A positive reaction to paraphenylenediamine in a patient with shoe dermatitis may, or may not, be significant as regards the presenting dermatitis.

Dermatitis from dyes in leather shoes is apparently extremely rare, and we have not encountered dermatitis due to this cause, except when the patient has had shoes *redyed*. The dye in redyed shoes is not likely to be as *fast* as the original dye. Two, of three patients, with "redye" shoe dermatitis cross reacted to paraphenylenediamine. In these cases the paraphenylenediamine sensitivity was significant, since it indicated cross sensitivity with the aniline dye used for the redyeing process.

While *primary* dye dermatitis in leather shoes is rare, such dermatitis with fabric or plastic shoes is encountered more frequently. We have studied several patients with shoe dermatitis due to dyes which *"bled"* readily from various nonleather shoes. Most of these patients also reacted to paraphenylenediamine.

In this connection it must be remembered that occasionally stocking dyes (especially nylon) will *"bleed"* from the stocking onto the lining of shoes. Patch testing with such "contaminated" shoe linings may be misleading because the sensitizing dye originally came from stockings. Even when stockings without sensitizing dyes are worn, dermatitis may persist for several months if the patient wears the shoes which have been "contaminated" with the stocking dyes. This is a type of *secondary* shoe dermatitis, the *primary* cause being the stocking dyes.

In our experience colored cloth linings in leather shoes have not caused dermatitis. Positive patch-test reactions with cotton shoe linings have to be carefully evaluated, since the sensitizing substance causing the reaction may have come from stockings or ingredients in deeper portions of the shoe. Dyes, chromates, and rubber chemicals may be leached out of shoes onto such linings. The fabric linings themselves, in our material, have not been sensitizers.

Role of Nickel Sensitivity in Shoe Dermatitis

In a recent review on contact dermatitis due to nickel we [10] pointed out that nickel is ubiquitous and that a constantly increasing number of patients are becoming sensitive to nickel. Although nickel sensitivity plays a minor role in shoe dermatitis, we have nevertheless encountered several patients who had dermatitis of the feet due to metallic nickel in or on shoes. We have, therefore, included a 5% nickel sulfate solution in our "screening" patch-testing shoe tray.

Three patients had dermatitis of the instep due to nickel in the eyelets of shoes. One patient had dermatitis caused by the metal tips of shoe laces which had been tucked under the tongue of the shoe. Contact of the foot with buckles made of nickel were responsible for shoe dermatitis in two cases. Nickel metal clips were the cause of shoe dermatitis in one case.

A positive patch test to nickel sulfate helped solve the cause of a dermatitis of the soles in one patient. This person occasionally wore nickel-plated arch supports. The dermatitis cleared when the metal arch supports were replaced by leather supports.

Nonspecific Factors in Shoe Dermatitis

It has been shown that perspiration can leach out chromates, rubber additives, and dyes from shoes and thus cause contact of these potential sensitizers with the skin. It is our impression that the use of a noncaking dusting powder (fluffy tannic acid,

boric acid, bentonite, and purified talc dispensed in a sifter box) may occasionally prevent dermatitis by reducing perspiration. Such a powder should be dusted freely into shoes and stockings. Not only does the dusting powder tend to lessen perspiration, but it also may act as a mechanical barrier to contact with the allergen. Some patients apparently tolerate certain shoes when their feet are relatively dry. Theoretically, it is conceivable that there would be no allergic contact shoe dermatitis without perspiration or moisture, and it is our impression that some of our patients can wear certain shoes without getting a dermatitis only when a drying dusting powder is used.

Other forms of mechanical protection against shoe sensitizers, such as the wearing of waxed paper, oiled silk, plastic paper bags, or aluminum foil inside shoes have been employed in the past. These protective agents have proved to be generally uncomfortable and unsatisfactory, since they are occlusive and hence tend to increase perspiration and maceration.

Other nonspecific factors, such as ill-fitting shoes and certain foot abnormalities, may cause excessive friction and wearing away of protective inner shoe linings and allow more intimate contact of shoe sensitizers with the skin. Also, orthopedic correction of various deformities or the wearing of special orthopedic shoes may be necessary to correct certain types of shoe dermatitis not necessarily of the allergic contact type.

Summary and Conclusions

In our case material of shoe dermatitis, rubber—either in the rubber thermoplastic box toe or in the rubber cements—has been the commonest cause of allergic contact dermatitis. This rubber sensitivity is apparently most often due to additives, such as the antioxidants and accelerators. Chromates, dyes, and nickel also occasionally cause allergic contact shoe dermatitis.

The following materials which are suggested for a "screening" patch-testing shoe tray are discussed: thermoplastic rubber box-toe material, 1% monobenzyl ether of hydroquinone in petrolatum, 1% 2-mercaptobenzothiazole in petrolatum, 1% tetramethylthiuram monosulfide in petrolatum, 0.25% aqueous potassium dichromate, 2% paraphenylenediamine in petrolatum, and 5% aqueous nickel sulfate solution. Details are given as to how to obtain these materials and how to prepare them for patch testing. Use of such a shoe tray may facilitate the diagnosis of allergic contact shoe dermatitis and obviate the necessity for the dissection of shoes to obtain materials for patch testing. However, negative reactions to the materials in the patch-testing tray do not necessarily exclude shoe dermatitis. It may be necessary to test with materials from the suspected shoe.

The names and addresses of shoe manufacturers and retailers are given from whom shoes may be obtained which are free from certain known specific sensitizers.

The role of such nonspecific factors as perspiration, friction, and orthopedic deformities also is discussed.

45-14 48th St.

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A Contrast of Cutaneous Cancer as Observed in Texas and in Minnesota

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Previous chemical studies in cancer of the skin have usually been drawn from homogeneous material: patients from a single public or private clinic or, less often, from the private practice of single or associated persons. A few participants in panel discussions have concluded that some difference in opinion on panels or in publications may have resulted from different backgrounds of clinical experience. Largely for these reasons we have compared two series of patients from our widely separated practices, beginning the study from curiosity and interest and only later considering public presentation of the results.

Contrasts between the clinical material of the two practices are based principally upon the geographic influence of situation in the northernmost and southernmost areas of the United States—Minnesota and Texas. In these regions there is great difference in temperature and the total hours of clear sunlight, leading to the wearing of protective clothing in the North, with resultant protection against light as well as cold. The national origins of the patients' inheritance in the Minnesota practice are principally German, Scandinavian, and Irish and, in the Texas practice, German (of blonde coloring), English, and Mexican or of Mexican descent. At the onset of the study it was assumed that these might be the principal factors contrasting our clinical experiences.

Estimate of relative incidence of cancer was based on the frequency of the first diagnosis of cancer of the skin for that person in that office in relation to the total number of new patients seen in that office in a given period of time.* After consideration of difference in the sizes of the practices, based on the numbers of new patients of all types seen during the same calendar year, incidence of patients with cancer was found relatively more frequently in the South, in the ratio of 5.7:1. Two factors lead to an even higher ratio of true incidence of cancers of the skin. In the South there is greater simultaneous multiplicity of lesions. More patients in the South develop additional cancers subsequently and thus return as old patients with new cancers; such patients, having a previous diagnosis of cancer in our offices, were not included in this survey.

For detailed review there was selected from each practice a consecutive series of patients with cancer, the periods of time being in the ratio of 6:1 in order to provide aproximately equal numbers in the two series. Before detailed analysis, the following northern cases were excluded: one patient with malignant melanoma, one with carcinoma metastatic from within the body, one with eccrine poroma, and one with basal-cell epithelioma derived from a nevus syringadenomatosus papilliferus. In the southern series a patient with malignant melanoma was included because he simultaneously had an epithelioma (but the melanoma was disregarded in the study). In the northern practice the clinical features were not known in five instances referred

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* Patients included in the study included those seen by the clinical associates in our practices—Orville E. Ockuly, M.D., and Arthur C. Ressmann, M.D., respectively.

for radiotherapy after recent complete excision; these patients were reviewed in all respects other than the gross morphologic features of their lesions. The compared series then included 200 patients, 99 from the North and 101 from the South. Not every point under consideration was available for review in the case of each patient.

Sex Ratio

Of the northern series the majority were women (54 women versus 45 men); in the South the ratio was reversed (59 men versus 42 women). The preponderance of southern men is presumably based on their greater actinic exposure as contrasted with northerners of both sexes and contrasted with southern women. It is not clear why the northern series includes more women than men; difference in actinic exposures of the sexes probably is not great and may be in the reverse order. In the older age groups there are throughout the nation more women than men as a result of a differential in longevity; this difference is probably not sufficient to explain the sex ratio reported here.

Number of Lesions

Ninety-nine northern patients presented 108 lesions, two patients having three lesions and five having two lesions; one young woman presented "numerous" superficial pigmented basal-cell epitheliomas. One hundred one southern patients presented 129 lesions, two having 6 lesions each; three with 5, 4, and 3 lesions, respectively, and nine with 2 lesions. The likelihood of multiple lesions is clearly greater in the South.

Multiple lesions were more frequent in men in both series, and in the Minnesota series they occurred in the eighth decade. On a given patient they usually were of similar histologic nature.

Among women the only squamous-cell epitheliomas on the lower lip were two on a Texan. Two squamous-cell lesions (one of which was on the hand) on a Minnesota woman occurred long after medicinal use of arsenic.

Previous Treatment

Forty-four of the southern patients had received previous treatment by their physicians for other cancers of the skin; histories in the northern practice were less exact, but only several had been so treated (excepting the five previously mentioned as having recent excision which resulted in their diagnosis).

Eight southern patients presented lesions which had previous treatment; in the North only one currently presented lesion had resisted previous therapy.

Size of Lesions

Because of difference in the use of descriptive terms it was impossible to compare exactly the clinical morphologic features. In the northern practice the dependence on routine use of biopsy probably accounted for less accurate clinical descriptions; the use of x-rays rather than radium perhaps led to less attention to the accurate measurement of lesions. Diameter of more than 1 cm. was estimated in 30% of the northern patients and 24% of the southern patients. After excluding the superficial basal-cell epitheliomas, a total of nine lesions in the north were more than 1.5 cm. in diameter; among the more numerous lesions in the south, the comparable figure was six. Of the larger lesions, two in the North were 3 cm. in diameter and one in the South was 3 by 4 cm.

We are uncertain as to the cause of this tendency for northern patients to present larger lesions. Possibly the northern person and his family, having less experience with cancer of the skin, fail to recognize it as early as it would be noticed in the South. Perhaps the southern patients come earlier to the dermatologist because discomfort follows their greater actinic exposure, with stinging or burning sensation in their keratoses. (However, the observations for this study were made in midwinter.)

Histopathologic Types

Biopsy was routine in the North, but in the South it was performed in only 25% of the lesions, when clinical features left doubt in the mind of the observer. There was one intraepidermal squamous-cell epithelioma in the northern series. In each, the northern and the southern series, there were five patients with superficial basal-cell epitheliomas. Other forms of basal-cell lesions were slightly more frequent in the North, 80% as compared with 75% in the South. Lesions with mixed basosquamous elements were observed three times in the North and once in the South; for this study these lesions have been regarded as squamous-cell epitheliomas. Although squamous-cell lesions occurred more often in the South, they were present in nearly the same proportion among men in both series, 26% in the southern and 28% in the northern.

The greater predominance of basal-cell lesions in the northern series was due partly to the larger number of women in the northern than in the southern series (since women in both series had more basal- than squamous-cell lesions) and due also to a greater tendency for northern women to develop basal-cell lesions (85% of the women in the North as compared with 75% in the South). This observation does not mean that basal-cell epitheliomas were more frequent in northern than in southern women but only that when epitheliomas occurred in southern women they were squamous-cell in type more often than they were in northern women. Since male Texans had squamous-cell epitheliomas much more often than did male Minnesotans but in no greater ratio than their preponderance of basal-cell epitheliomas, these observations are somewhat confusing as to the influence of actinic rays in the production of basal-cell epitheliomas. However, since both types of epithelioma are much more frequent in the South, it is possible that actinic radiation is an etiologic factor in both, as appears to be true in radiodermatitis and xeroderma pigmentosum.

Sites of Lesions

Comparison of sites of involvement showed variations, some of which were difficult to explain. Lesions on areas normally covered by clothing were present in about the same proportions in both series, four in the North and five in the South. In each series one man and one woman presented a squamous-cell epithelioma on a hand. Thus approximately 95% of the epitheliomas were on the head and neck. Lesions of the scalp were more frequent among women, an observation for which we have no explanation.

In absolute figures for basal-cell epitheliomas the cheeks, nose, and eyelids were favored sites in the North, as were the cheeks, nose, and forehead in the South. Comparing northern and southern series the cheeks and nose were relatively (not absolutely) more frequently involved in the North; the forehead was more frequently involved in the South, both relatively and absolutely.

Except as open collars allow greater exposure to actinic radiation of the neck in the South, we cannot explain the differences in incidence relative to site. One might have expected the hands to present a greater number of lesions in the South.

Ages of Patients

No attempt was made to compute the age at time of onset of the lesion; the stated ages are as at the time the patient presented for treatment and the ages were grouped by decades. Median age in the southern series was nearly 10 years younger. When considered separately for basal-cell lesions (50-59 years versus 60-69 years) and for squamous-cell lesions (60-69 years versus just more than 70 years), one notes that the basal-cell lesions were observed earlier in both series.

In the southern series the basal-cell lesions were presented by women at an earlier

age; squamous-cell lesions were presented earlier by the southern men. In the northern series the age-sex trends were similar but less pronounced.

Southern men had many more squamous-cell lesions of the neck and the lower lip, as compared to southern women and to northerners of either sex. Therefore, conclusions should not be drawn without giving consideration to the fact that these sites were associated with earlier ages (both in the North and the South in the case of the lip). Thus, if one excludes squamous-cell involvement of the lower lip and neck, it appears (1) that other squamous-cell lesions were associated with ages that comparatively were even higher than suggested above and (2) that there was in the South no age difference between the sexes as regards squamous-cell lesions of sites other than the lower lip and the neck. The difference between ages of northern and southern patients could be assumed to relate with actinic exposures in the cases of both types of lesions.

Treatment

There was no attempt to compare the results of therapy. The following tabulation displays the selection of therapeutic agents in the two series:

	Radium	X-Rays	Electro-surgery	Excision by Scalpel	Total
Texas	100	12	14	3	129
Minn.	0	86	16	5	108 †

This multiplicity of therapeutic agents is evidence of the dermatologist's opportunity for individualization of therapy by selecting from various alternatives in order to obtain for his patient the best possible result. In addition to this ability and willingness to use a variety of therapeutic agents the dermatologist is in a particularly favorable position for management of the problem of cancer of the skin because of his knowledge of clinical differential diagnosis, his training in and use of histopathology, and his interest in precancerous lesions.

Comment

We have presented comparative figures on the incidence of cancer of the skin in our practices. These figures only suggest the true incidence in our communities. After consideration of these figures, the greater multiplicity of lesions on the Texan patients and their greater susceptibility to the future development of additional lesions, one estimates that the ratio of 10:1 more clearly represents the relative incidence of cancer of the skin in the two communities.

The greater incidence of epitheliomas in women versus men in the North is not explained by us.

The larger size of lesions in the North was suprising.

The ratio of basal-cell to squamous-cell epitheliomas was higher than anticipated on the basis of previously published reviews, 4:1 in the North and 3:1 in the South. The relative incidence of squamous-cell epitheliomas was similar in both groups of men. The greater incidence of basal-cell epitheliomas among women versus men in the northern series led to the higher total incidence of epitheliomas among women in the northern series. No explanation is offered.

Involvement of the head and neck approximated 95% in these as in other series. In both series the cheeks and the nose were favored sites for basal-cell epitheliomas, with the forehead next in line in the Texas series and the eyelids in Minnesota. Greater exposure of the forehead to sunlight might be the explanatory factor. This factor may also account for the greater involvement of the neck by squamous-cell epitheliomas in the Texas group, but, in Minnesota, where the cheeks and nose were more often involved, it fails to explain the relatively smaller involvement by cancer of the lower lip.

Occurrence at relatively early ages was noted in cancer of the lip and neck as

† One patient was referred to Dr. Frederic E. Mohs, University of Wisconsin, for chemosurgery because of a large lesion on the nose.

compared with squamous-cell epitheliomas elsewhere and with basal-cell epitheliomas. With both basal- and squamous-cell epitheliomas the Texans were involved at earlier ages than were the Minnesotans.

Summary and Conclusions

Cancer of the skin was observed much more frequently in Texas than in Minnesota. Both types occurred at earlier ages in Texans than in Minnesotans. Basal-cell lesions occurred more frequently in women. They occurred at earlier ages than did squamous-cell lesions other than those of the neck and the lower lip, which were seen almost exclusively in men and relatively more frequently in Texans.

Actinic exposures appear to explain these differences, but they do not explain completely the behavior of basal-cell epitheliomas. If basal-cell epitheliomas relate with actinic exposure, then why do they occur earlier in women than in men? Greater actinic exposure is not likely to be great enough for the complete explanation. However, difference in actinic exposure may be at least part of the explanation for greater absolute, not relative, incidence of basal-cell epitheliomas in Texans, the occurrence there at an earlier age, and the relatively greater incidence of such lesions on the forehead, as compared with Minnesota.

350 St. Peter St., St. Paul.

ABSTRACT OF DISCUSSION

Dr. Everett C. Fox, Dallas, Texas: Dr. Lynch, Dr. Lehmann, and Dr. Pipkin have presented an interesting comparative clinical study. Further studies of this type may encourage more uniform clinical records and terminology, the verification of results of various therapeutic measures, and the development of a better understanding of regional variations of common disease entities.

The ratio of 6:1 or 10:1 for cutaneous malignancies in Texas and Minnesota seems to be in agreement with general opinion. The size and the location of lesions were much the same.

The 10-year age difference probably relates to many factors and not to solar activity alone. The occurrence of squamous-cell carcinoma more frequently in the South very probably relates to a greater actinic exposure, and the lesions occur at an earlier age. This certainly contributes to the development of lesions on the sides of the neck and lip. Herpes simplex of the lip frequently precedes carcinoma of the lip.

In general, it is doubtful that basal-cell carcinomas have any relation to solar exposure, even though 85% of basal lesions occur above the clavicle. This is also the area of highest pilosebaceous activity. Keratoses usually precede the development of a squamous-cell lesion. The basal-cell lesion has no antecedent in the vast majority of cases and is frequently follicular in site. Seborrhea is probably more important than sunlight. However, basal-cell lesions are seen to occur in areas of radiodermatitis, and they usually, again, are follicular, beginning as a 1 or 2 mm. firm vesicle-like lesion. Basal-cell lesions are usually present in 75% to 85% of cutaneous malignancies.

A recent review of 150 patients' records revealed basal-cell carcinoma in 128, which was 85% of the cases, with 80 men and 48 women, and squamous-cell carcinoma in 22 instances, which were 15% of the series, with 18 men and 4 women. In this group there was also one melanoma in a man.

The increased incidence of basal-cell lesions in women, observed by Dr. Lynch, has no immediate explanation unless a greater number of female patients are seen.

We should encourage these gentlemen to pursue their clinical differences of findings and provide us with answers to some of these perplexing questions.

I believe that in large series of cases, if we could agree on a accurate standard clinical record to record all of our information, with standard nomenclature, and this information could then be transferred to IBM punch cards for statistical studies, this might enable us to study some of these peculiar and now unanswered questions.

Dr. Leslie M. Smith, El Paso, Texas: I should like to emphasize a few points made by the essayists which are particularly applicable to practice in the very arid section in which I live.

The authors reported that in Texas epitheliomas occur earlier than in Minnesota, as well as being much commoner. That is certainly true. We have observed a number of squamous-cell epitheliomas of the lower lip in red-headed freckled cowboys at around 18 to 21 years of age. These were men who smoked a lot, so that was a factor in addition to the sun and the extremely dry air.

Our big problem in the desert country is the chronic keratotic actinic skin, the people in outdoor occupations who do not tan uniformly but freckle. These people come in more or less regularly with multiple epitheliomas, both squamous and basal, on the face and neck, and keratoses and squamous-cell epitheliomas on the backs of the hands. They are

regular patients as long as they live. Some of these patients have a thick leathery keratotic skin, particularly on the hands and forearms, and these usually have a low tolerance for radiation. Often some form of surgical treatment in these cases is preferable.

DR. HERBERT S. ALDEN, Atlanta: This very interesting comparison brings up some ridiculous notions, perhaps, as well as some serious ones. One might even suggest that segregation may explain this quantitative difference, but I do not think that it is so much a geographical fact as it is an intensity of solar radiation, as well as a prolonged intensity of solar radiation. Certainly, in Georgia, we see far more basal-cell carcinomas rather than squamous-cell carcinomas. I think that the overwhelming majority of the squamous-cell carcinomas of the lower lip occur in farmers, many of whom give a history of a prior fever blister. I am also impressed by the fact that the existence of seborrhea is a potent factor. This discussion also brings up the point of the "basal-cell nevus," of which Dr. Howell wrote. Is it possible that some of these are hereditary tumors?

DR. LOUIS H. WINER, Beverly Hills, Calif.: For ten years I have been treating three test pilots who have developed multiple cancers. These cancers are most frequently basal-cell cancers. They develop not only on the exposed parts but also on the unexposed parts of their bodies. I have considered cosmic rays as a contributory factor in the formation of these skin lesions because these men fly at very high altitudes.

I also have seen patients with herpes simplex of the lip who three or four weeks later come in with a nodule which had not been present before, in the same site of the lip. On biopsy, the nodule is proven to be an intraepidermal squamous-cell carcinoma. Could the herpes have produced these abnormal cells? We find hyperchromatic single, as well as multinucleated, cells in smears of herpes vesicles. These cells may resemble very closely those seen in smears of exfoliated cells of a squamous-cell carcinoma. By knowing the clinical history and the site of the lesion, one can diagnose these smears as abnormal herpes or balloon cells. In the biopsy specimen of these nodules, however, the entire epidermal rete is dissociated, the polarity of the nuclei are disarranged, and abnormal mitotic figures are present. One can, therefore, consider these as malignant carcinoma cells, rather than the degenerated balloon cells of herpes.

DR. JAMES B. HOWELL, Dallas, Texas: This is a very popular subject, and dermatologists should continue to take the initiative in the field of skin cancer. Dr. Michelson has recently suggested that a tumor registry be established by the American Academy of Dermatology. This would give an opportunity to continue a study of the type started by Dr. Lynch, Dr. Lehmann, and Dr. Pipkin. I think we should give weighty consideration to the matter of a central tumor registry for cutaneous tumors.

DR. WILEY M. SAMS, Miama, Fla.: There are many points of interest in this comparative clinical report. Difficulties are encountered from the statistical standpoint in a problem of this type, and many factors must be considered in the selection of patients in order that a study will correctly evaluate the various clinical points under discussion. Dr. Pardo-Castello and I have discussed the fact that we both see patients from Key West, Fla. It is a community approximately midway between Miami and Havana, insofar as transportation facilities are concerned. It has a large group of both English- and Spanish-speaking residents. Owing to my linguistic restrictions, I see mainly the English-speaking group, and it is likely that Dr. Pardo sees more of the Spanish-speaking group. I suspect that my English-speaking group has a higher incidence of skin cancer. In this situation, geographical location is not so important as the racial factor.

Reference is made to Dr. Lynch's higher percentage of female patients. Factors which might lead to the choice of a physician by patients who are seeking their medical consultant are multiple: The method of treatment ordinarily used, fear of surgery, hospitalization vs. ambulatory treatment, insurance programs, and the financial status are just a few to be considered. I am certain that the practitioner sees a different class of patient and earlier manifestations of neoplastic disease than that which occurs in the clinic group from the same community. How to set up a statistical study to evaluate all of the factors is the problem that faces us in a study of this type.

DR. MARION B. SULZBERGER, New York: If it had not been for the remarks of Dr. Wiley Sams and Dr. Everett Fox, I should not have spoken. But now I should just like to report that, starting about three years ago, we began at the Skin and Cancer Unit of the New York University-Bellevue Medical Center a statistical analysis of different types of tumors, particularly cancers of various kinds.

Some years ago I was struck, as all of us have been, by the fact that this tremendous clinical material of all kinds of skin tumors was going through our institution but was valueless as far as any statistical compilation or comparative therapeutic evaluation was concerned because no proper records, no proper index, had been set up for analyzing the cases from the various important points of view.

Under Dr. Victor Witten and Dr. Alfred Kopf and the surgeons, first Dr. Herbert Willy Meyer and later Dr. David Lyall, Dr. Alexander Zimany,

and others; under the radiologists, Dr. Milton Friedman and Dr. Gustave Kaplan, and under the general pathologists of Dr. Maurice Richter's Service we now have a tumor clinic, a tumor section, and a tumor conference in which these tumors are all classified and their different characteristics very carefully recorded on IBM cards.

There are several hundred different factors being recorded on these IBM cards, and the American Cancer Society has been very helpful to us, and their statisticians also, in setting up the basis for this statistical study. I should certainly welcome it if other clinics or practitioners and other dermatologists would augment our studies and come and see what our records are on these cases and how hopeful the outlook is for us to be able to find out something, maybe in the next 20 years, about these tumors—certainly something about their course and their responses to various forms of therapy and perhaps even about their causes.

I should also like to mention that this study has been supported by several grants; some smaller grants and one very generous grant from the Lillia Babbitt Hyde Foundation.

DR. GEORGE H. CURTIS, Cleveland: I think that it is most interesting that this discussion on establishing a tumor registry seems to conform somewhat to the suggestion I made yesterday about establishing a central registry for all dermatological diagnoses.

In The Cleveland Clinic we have a tumor registry in which we follow up malignancies of all types. In regard to the basal-cell epitheliomas in our registry, we follow up these patients for three years and the squamous-cell lesions for five years. We do this in conjunction with the Committee on Cancer of the American College of Surgeons and the Joint Committee on Accrediation of Hospitals.

I should like to know from the membership as to whether or not a three-year follow-up is long enough for basal- and a five-year follow-up long enough for squamous-cell lesions.

DR. STEPHEN ROTHMAN, Chicago: In reply to Dr. Curtis, at the University of Chicago our Cancer Registry follows all patients with basal-cell carcinomas, squamous-cell carcinomas, and anaplastic keratoses for five years. I think that this is the specification of the American Cancer Society. We are gratified with the work of this registry because it automatically calls in the patients for a check-up every year.

Concerning the occurrence of herpes simplex followed by squamous-cell carcinomas on the lip in the same place, I should like to call your attention to old data in the literature. When I collected data concerning cutaneous manifestations of internal malignancies many years ago in Dr. Bruno Bloch's clinic, in Zurich (ARCH. DERMAT. U. SYPH. 149:99, 1925), I found many cases where herpetiform lesions, zoster or other herpetiform lesions, had preceded cutaneous metastases of internal carcinomas; so we must admit at least as much that a locus minoris resistentiae has been created or can be created by herpetiform lesions.

DR. A. FLETCHER HALL, Santa Monica, Calif.: I have been much interested in this presentation and in the remarks of the previous discussers.

I think that if we take into consideration what Dr. Fox said with regard to a great many of the basal-cell carcinomas as being probably *not* of actinic origin and that consequently there is a substratum of nonactinogenic carcinomas in both regions and then superimpose upon that substratum the number and type of actinogenic carcinomas (obviously more frequent in Texas), we get a better explanation of the shift in the types as reported in the two geographic areas.

The other point that I wanted to comment on was with regard to herpes simplex preceding carcinoma of the lip. I do not think that we can or should assume that there is any causal relationship in this sequence because if we have two actinogenic diseases which can affect the lip, naturally, we will find both of them occurring in the same person in many cases, and I do not think we have any right to assume that herpes is a premalignant lesion on this basis alone.

DR. SAMUEL AYRES III, Los Angeles: I was somewhat surprised to hear the authors report that the effect of actinic damage was not particularly important in the etiology of basal-cell carcinomas. I had always felt that there was a very definite relationship and that the much lower, in fact almost negligible incidence, of either type of skin cancer in darker-complexioned races was compatible with that idea. I should like to get their ideas on the apparent discrepancy between the difference in incidence of basal-cell carcinomas in the different types of complexion, on the one hand, with their feeling that there was no connection or, at least very little connection, with sunlight exposure in relation to basal-cell carcinoma.

It seems to me that we see basal-cell carcinoma in very high incidence in the same patients who also have actinic keratoses, apart from the development of squamous-cell carcinoma.

I should also like to point out that the question of what is considered the covered portion of the body, I think, must undergo considerable revision. Certainly, it depends to a large extent on the area of the country in which you live and, perhaps, also to which generation you belong. Certainly, in many of the sunny areas of the country, particularly southern California, you are hardly justified in considering anything except the immediate bathing-trunk area in men and the swimming-suit area in women as covered portions. I think that statistics, in order to be at all standardized, would have to

take into account the fact that large amounts of sunlight are certainly inflicted upon the back, arms, and legs in many persons, certainly in our area of the country.

DR. HERMAN PINKUS, Monroe, Mich.: Most dermatological publications on skin cancer come, of course, from large centers and from experts especially interested in this field. Some years ago I attempted to do something about the contention of surgeons and radiologists that favorable therapeutic results reported from these sources did not prove that the average dermatologist is competent in treating skin cancer. Dr. Richard Ferrara, at that time a resident in our department, reviewed five-year treatment results in 226 cases treated in the private offices of five Detroit dermatologists. There was no selection of cases except that all had microscopic confirmation of the clinical diagnosis. Therapy varied considerably according to the preference of the individual dermatologist. Surgery, x-ray, and dermatologic curettage, and cautery were employed most commonly. Results were surprisingly uniform in that about 95% of cases were cured without recurrences. This survey indicates that the average dermatologist in the Detroit area is entirely capable of curing skin cancer.

Last year I compared the age distribution of basal-cell epitheliomas in my biopsy material and found that average age at the time of consultation had decreased noticeably when the years 1945-1946 and 1956-1957 were compared. The peak was still in the sixth decade, but many younger patients were seen. I doubt that people develop basal-cell epitheliomas at an earlier age now than they did 10 years ago. I rather believe that education of the public actually leads many patients to the dermatologist several years earlier than they came in times past. Many of the biopsied lesions were quite small and noncharacteristic clinically. This experience puts added responsibility for early diagnosis on the dermatologist (A.A.A.S. symposium in skin malignancies, to be published).

DR. C. FERD LEHMANN, San Antonio, Texas: It must be reiterated that this comparison of the incidence of skin cancers in the North and South does not give a true incidence of the disease in general. To do so, we would have to record the experiences of all practitioners in every field, as well as the statistics from all hospitals and clinics. This is only a comparison of the practice in one office in the North with one in the South.

Regardless of the small series in this study, I feel that the ratio of 10:1 correctly reflects the increased number of skin cancers seen by dermatologists in the southwestern United States. It is regrettable that our records are not complete enough to make further comparisons. I should be particularly interested to compare the number of keratoses seen in each cancer case in the two series. I would estimate that each cancer case seen by us had an average of five keratoses on the exposed parts; in other words, five keratoses to each active cancer. Strong sunlight produces a stinging or burning sensation in keratoses, and, very frequently, the doctor is consulted for this reason and the cancer is discovered incidentally.

Our series was not collected during the keratosis season, which is July, August, and September. This facet could be studied further from various standpoints. For instance, first, should every advanced keratosis be biopsied to corroborate definitely the clinical diagnosis? In our work, this is not feasible, for very obvious reasons. Therefore, we probably coagulate many superficial cancers as keratoses. Second, what is the ratio for the number of keratoses in the cancer case which is first seen to new cancers that later develop? In other words, does the man who develops all these keratoses not have a propensity to develop cancer, regardless of sunlight? Third, what is the ratio of keratoses in people of outdoor occupations to people not excessively exposed to sunburning? We have partially answered that. Fourth, what proportion of cases of skin cancer later develop internal cancer? That question needs further studies in the South.

Again, our records do not give accurately the proportions of blondes who had skin cancer, although partially so. It is my estimate that the ones who had outdoor occupations are in a ratio of five blondes to one brunette. We rarely see cancers in Mexicans and Negroes.

Another question that has been in my mind for years is, do our patients have some other common carcinogen than sunlight irritation? Could it be dietary? That has to be considered in these people who live in this realm of civilization. Or do they weaken the coenzyme system of their cells by restriction of an essential vitamin or trace element? Or is there a common external carcinogen other than sunlight, such as the alkali dust irritation or an end-product of sebum that becomes photodynamic? Remember, a lot of these people who live out on ranches and farms do not practice the best hygiene in their skin.

Then, finally, does atavism explain the increased incidence of skin cancer in our locality? In other words, have our patients inherited defective protoplasm?

After considering the above-mentioned questions, one can readily see that skin cancer in the sunny Southwest presents some interesting problems which require further study.

DR. JAMES LEWIS PIPKIN, San Antonio, Texas: Possibly, the discussion precipitated by this paper makes it worth while. The comparison of the carcinomas encountered in our private practices in these limited short-time surveys brings out very

interesting and unsuspected differences. Some are explainable, and others are not.

The frequency in the South as compared to the North, say 6:1 or 10:1, whichever figure you elect to go by, is probably still a low figure. In our survey, we, unfortunately, picked two months which we might term as "out-of-season months" for cancer, that is, January and February, 1955. At that time, we saw only 129 carcinomatous lesions in 101 patients. During these months, the detailed data were recorded for this survey. Approximately twice as many patients with carcinomas were seen during the same length of time between May 1 and through October, 1955, which, incidentally, may be considered our "open season" on skin cancers. A total of 631 patients with skin cancer was treated during this six-month period; in other words, over 1,200 skin cancers were treated during the year 1955.

If the average of 100 lesions treated a month is used as a comparative figure, the ratio would be 13:1 in favor of the South. This can be further enhanced if one leaves out the Latin-American population, who are deeply pigmented, which in turn affords protection from the actinic rays, thereby lowering the incidence of skin cancer.

In regard to size, Texas concedes to Minnesota. It is difficult to explain why the northern patients present larger lesions. As Dr. Lynch intimated in his discussion, it could possibly be that the northern patient, having less experience with cancer of the skin, fails to recognize it as early as in the South. It is well to remember that 44 of our 101 patients had previously been treated for cancer of the skin. It is generally felt, I believe, that most skin cancers seen today are smaller than those observed in years past. No doubt, the comprehensive educational campaign sponsored by the American Cancer Society and the propaganda put forth regarding the early warning signs of cancer by the press, the radio, and television tend to bring the patient, and especially the patient who has had previous experience with cancer, to the physician earlier.

Large lesions are more frequently seen in the ignorant and financially distressed patient. This is casting no aspersions on the Minnesotans, however. It is also true that many of these large lesions are now being treated in our state by the state-operated tumor institute and are not commonly seen by the private physician.

Distances in Texas incur trouble and expense, both of which are, indeed, a deterring factor to the ignorant and the poor patient to travel from their community to the distant tumor hospital. This would tend to increase the small lesions in our series.

This particular presentation can be considered a pilot study and indicates differences do exist in skin cancer in various locales. This report may possibly act as a stimulus for a more comprehensive study of a larger series of cases over a longer period of time, which might, in turn, clarify these differences.

With regard to Dr. Ayres' question, this short statistical survey does not indicate that sun has very much to do with the production of basal cells. However, Dr. Lehmann and I feel very strongly that actinic rays do play an important part in stimulating the onset of basal-cell carcinoma in our locale.

The Comparative Effect of Various Wet Dressings upon Aseptic Cutaneous-Wound Healing in Man

RAY O. NOOJIN, M.D.; ROBERT A. LEWIS, M.D., and CHARLES H. LUPTON, M.D., Birmingham, Ala.

Wet dressings are an effective dermatologic tool frequently used for multiple purposes—bacteriostasis, debridement, relief of pruritus, mechanical protection, application of heat and cold, keratolytic action, and healing effect.[1,2] Since many different solutions are applied empirically by physicians in the form of wet dressings, a study was undertaken to determine the comparative effects of several solutions upon aseptic wound healing in man. Except for aseptic wound repair, no other facets concerning the use of wet dressings will be discussed.

Standard textbooks of pathology describe wound healing and are generally in agreement as to the processes concerned.[3-5] These texts explain that in the open type of wound (without close juxtaposition of wound edges) the gap is filled with a mixture of coagulated blood, fibrin, and inflammatory exudate, and in and upon this the fibroblasts and endothelium build granulation tissue. The process of granulation tissue formation begins at the base of the wound and progresses to the surface. Polymorphonuclear leukocytes are seen early and are soon followed by macrophages and lymphocytes.[4]

New epithelium regenerates from the sides of the wound from normal epidermis by a "sliding out" process across the granulation tissue, with mitosis taking place in the older epithelium some distance from the edge of the injury.[5-7] It is felt by one author that in order for epithelium to migrate a substratum of mesenchyme is required.[3]

Gillman et al.[8] offer a somewhat different viewpoint. Their concept states that the first tissue to regenerate and bridge the incisional gap is the epithelium and that this epithelium always inverts and grows into the depth of the wound. Four to six days after injury there develops just beneath the new epithelium a dermal response in the form of a glycogen- and protein-rich exudate. This exudate raises up the overlying epithelium in blister-like blebs. On the 6th-10th days there is seen an infiltrate of numerous round cells beneath the new epithelium as well as capillaries growing into the subepithelial exudate. Reticular fibers are also deposited. These authors, in addition, aver that connective tissue regeneration takes place from blood cells which migrate into the subepithelial exudate from the blood stream itself and from the previously occurring perivascular cuffing of round cells and not from activation of existing dermal fibrocytes. Too, they believe that the blood and tissue fluid released at the time of wounding play no role in repair other than in a protective fashion.

By using Thiersch's donor sites Gillman et al.[9] found that new surface epithelium regenerated from neighboring undamaged skin, hair follicles, and sebaceous gland ducts. The outgrowing epithelium forms "pseudorete pegs" which invade the dermis. These invading spurs of epithelium become detached; are surrounded by lymphocytes, histiocytes, and fibrocytes, and eventually are treated like foreign bodies. The authors concluded that wound healing was dependent upon the maintenance of a delicate balance

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between new connective tissue and regenerating epithelium, with each, in turn, influencing the other.

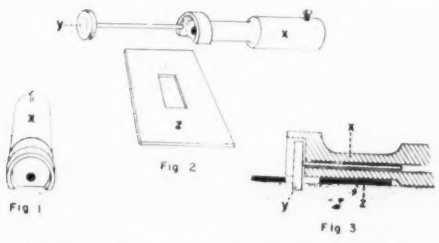
Dunphy and Udupa divide the normal pattern of wound healing into two phases: The first is a productive or substrate phase, beginning shortly after wounding, with a duration of approximately five days.[10] During this phase mucopolysaccharides and soluble protein precursors of collagen are produced. The second phase follows and is the collagen phase, wherein normal collagen fibers are produced. This continues until healing is complete.

A perusal of the more recent literature did not reveal any study of the effects of wet dressings and various compress materials upon wound healing. Randall and Randall[11] used the abraded skin of rats to investigate the effect on wound healing of various preparations; however, none of these was used in the present study. They found that reepithelization of abraded skin varied inversely as the degree of irritability of the substance applied. Such substances as scarlet red were found to be irritating and consequently retarded wound repair.

Material and Methods

In order to make comparative studies of the effects of various solutions upon the elements involved in wound repair (reepithelization, cellular infiltrate, elastic tissue, collagen, polysaccharides, and other carbohydrates), both histologic and histochemical methods were used.

Six hospitalized patients with nondermatologic disorders were utilized for study (five Negro women, ages 30, 34, 39, 40, and 50 and one white man, age 32). None of these had received or were receiving steroid therapy.



Figs. 1, 2, and 3.—Brass guard and handle for holding diamond-cutting tool. *X*, brass guard and handle control depth of wound. *Y*, cutting tool flat-edged wheel type diamond instrument 0.25 cm. × 1.25 cm. *Z*, flat stamped brass plate with central opening sufficiently large to control length and width of wound.

On the posterior thoracic region of each patient, six abrasions (2 cm. long × 0.5 cm. wide × 2 mm. deep) were made approximately 6 cm. apart. A dental S. S. White Clinic Type Bench Motor with diamond-cutting tool which operated at 3,000 rpm was used to make the abrasions (Figs. 1, 2, and 3). For the cutting tool a flat-edged wheel type diamond instrument 0.25×1.25 cm. was used. The wound was made aseptically, and ethyl chloride was used locally for anesthesia. A flat stamped brass plate was employed with a central opening sufficiently large to control the length and width of the wound. A guard partially covering the cutting wheel would not allow a cutting depth over 2 mm., or to about the mid-dermis (Figs. 1, 2, 3).

Wet dressings were applied to five of the six wounds continuously for eight hours each day for five consecutive days. The untreated lesion served as a control and was protected with a perforated plastic cup. The dressings were wet sterile cotton gauze sponges and were removed every hour for eight hours, after which a new sterile freshly wet dressing was reapplied. Each dressing was covered with clear plastic sheeting slightly larger than the wet dressing and held in place by rubber bands attached to adhesive-tape moorings. Aluminum acetate (Burow's) solution 1:20, potassium permanganate 1:4,000, urea 3%, isotonic saline, and sterile water were the five preparations used. Each agent was sterile when applied. When the wet dressings were removed at the end of each eight-hour period, all wounds were covered with a dry sterile cotton gauze sponge; only during this period was the patient allowed to lie on his back.

At the end of 72 hours a surgical biopsy specimen was removed from the lower end of each wound under 1% procaine local anesthesia. Wet dressings were resumed, and on the fifth day similar specimens were excised from the superior portion of each wound. One-half of each specimen was fixed in absolute alcohol and refrigerated at −14 C until prepared histologically; the other half was fixed in neutral buffered 10% formalin without refrigeration.

After the fifth day all wounds were covered with sterile cotton gauze sponges and were redressed daily until completely healed. All wounds were completely healed clinically by the 10th postoperative day.

Four histologic staining techniques were selected to demonstrate the more important aspects of wound healing, namely, the general morphology, collagen, elastic tissue, and carbohydrates, including the acid polysaccharides. The hematoxylin and eosin stain was employed to demonstrate the general morphology. Carbohydrates were shown by the

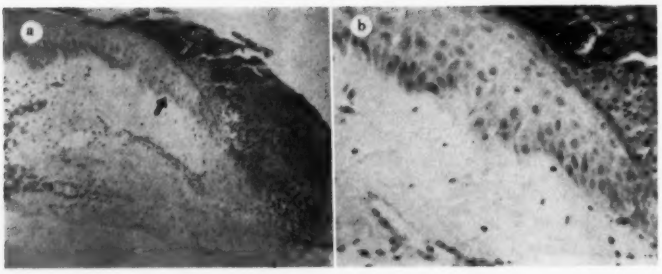


Fig. 4.—(*a*) Section of edge of wound on third postoperative day. Arrow denotes down growth of epithelium progressing under crust. Hematoxylin and eosin; reduced approximately 45% from mag. × 100. (*b*) Higher magnification of epithelial projection seen on third postoperative day. Hematoxylin and eosin; reduced approximately 45% from mag. × 430.

use of the alcian blue-periodic acid-Schiff (AB-PAS) reaction.[12] The alcian blue stain shows acid groups, presumably polysaccharides. This, followed by the periodic acid-Schiff (PAS) reaction, allows simultaneous demonstration of acid groups and 1,2-glycols of polysaccharides. One-tenth per cent alcoholic toluidine blue was employed as a metachromatic stain for acidic polysaccharides.[13,14] The difficulties attending the use of toluidine blue limit its usefulness. Dry sectioning on some of the alcohol-fixed specimens was done to preserve as much as possible of the water-soluble carbohydrates. Collagen and elastic tissue were stained by the orcein-Van Gieson method.

An estimation of the amount of each histochemically detectable substance was made by grading the reaction from 1+ for faint staining up to 4+ for the most intense reaction seen. Epithelization at the wound site was also graded with this plus schema. A 1+ estimate signified beginning epithelization, whereas a 4+ estimate indicated complete reepithelization of the wound.

Results

Third Postoperative Day.—Generally, on the third day of healing there was seen microscopically an area of injury through the epidermis to the level of the mid-dermis, with normal tissue on either side of the wound. Covering the surface of the injury site was an eosinophilic amorphous material (hematoxylin and eosin stain) consisting of coagulum probably composed of plasma, fibrin, and tissue fluid extruded from the damaged tissue. In the gap between the edges of the wound was an eosinophilic material in which were many red blood cells and cells of the polymorphic and lymphocytic type. Normal connective tissue was seen below the injury, with a disarrangement and fragmentation of the collagen bundles at the junction between the crust and the base of the wound. No sharply demarcated line existed between the crust and the dermis. At the lateral borders of the wound short strands of epidermal cells (2 to 3 cells thick) were seen extending down to the dermis below the edge of the crust (Fig. 4). Epidermal mitoses were only rarely seen.

The crust, which contained plasma, fibrin, tissue fluid, an infiltrate of polymorphonu-

Fig. 5.—Section of wound on third postoperative day. Note that crust stains heavily because of the presence of periodic acid-Schiff-positive material. Alcian blue-periodic acid-Schiff stain; × 50.

clear cells and lymphocytes, and sloughed fragments of collagen and elastic tissue, showed positive PAS staining after the AB-PAS stain (Fig. 5). With the same stain and as noted by previous observers, the bordering epidermal cells of the mid-portion of the prickle layer contained scattered fine granules of pink material, presumably glycogen, in their cytoplasm.[15] Neither the basal cells nor the granular-cell layer had AB-PAS-positive material in their cytoplasm. Approximately the same amount of reepithelization was present in all wounds including the control. Just below the surface of the wounded dermis there was noted a well-scattered and diffuse blue-pink material when stained with AB-PAS. This stained a deeper hue than the surrounding normal uninjured dermis. These findings were similar in all treated lesions and the control.

The orcein-Van Gieson stain for collagen and elastic tissue showed a few black strands of elastic tissue and some red fragments of collagen in the crust. The area just beneath the crust in the dermis revealed the collagen bundles to be rather edematous, with some of the collagen bundles disoriented, lying almost perpendicular to the skin surface rather than paralled. No newly formed collagen or elastic tissue was noted.

The orderly events of recovery on the third day as shown by regenerating epithelium, increased amounts of polysaccharides and other carbohydrates, and equal amounts of cellular infiltrate indicated a comparable progression in all wounds.

Fifth Postoperative Day.—In the fifth day specimens the same general picture as on the third day was seen; in addition, tongues of epithelial cells were extending downward and outward over the base of the wound beneath the crust (Fig. 6). These extensions of epithelial cells were three to four times longer than those noted in the third-day specimens. They were two to six cells in thickness. Even though reepithelization was observed in all fifth-day sections, reepithelization in the control wound was more advanced than that of any of the treated wounds of four patients. In two of these the differences were great, and in two they were slight. In the two remaining patients epithelial regeneration appeared to be approximately equal in all treated wounds and the control.

All the fifth day biopsy specimens showed an equal amount of cellular infiltrate but a denser infiltrate of lymphocytes and particularly polymorphonuclear cells than was seen on the third day. Too, in all instances of the fifth day the crust showed a more pronounced separation from the dermis than on the third day.

The area of the dermis just beneath the junction of dermis and crust revealed some differences between the third-day and fifth-day sections. On the fifth day increased edema and clear spaces were noted in this portion of the dermis. In the edema fluid just beneath the crust were found some cells with spindle-shaped nuclei which appeared to be fibroblasts (Fig. 7).

Again, as on the third day, the crust showed a positive PAS reaction with the AB-PAS stain, which was equal in all the fifth-day specimens, and it appeared that the hue was deeper than on the third day.

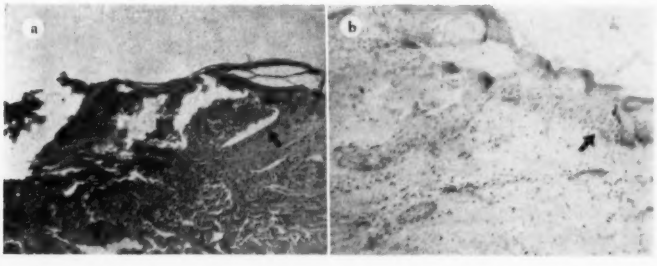


Fig. 6.—(*a*) Section of edge of wound on fifth postoperative day. Arrow denotes further growth of epithelium under crust. Hematoxylin and eosin; reduced approximately 45% from mag. ×100. (*b*) Section of edge of wound on fifth postoperative day. Arrow denotes epithelium. Hematoxylin and eosin; reduced approximately 45% from mag. ×210.

Fig. 7.—Arrow denotes fibroblast lying in the edematous superficial portion of the injured dermis beneath crust on fifth postoperative day. Hematoxylin and eosin; × 970.

A blue-pink color produced by this stain was seen in the edematous areas in the dermis just beneath the crust and was a more pronounced color than on the third day.

The mid-spinosum-cell layer of the epidermis adjoining the injury had all its cell cytoplasm literally filled with strongly PAS-positive granules—many more granules than on the third day (Fig. 8). All of the epithelial cells which projected under the crust covering the wounded dermis had their cytoplasm filled with PAS-positive material, and all resembled the PAS-positive cells lying in the middle of the adjacent prickle-cell layer. This finding was consistent in all the fifth-day specimens.

No differences were detected in the collagen and elastic tissue stains of the fifth-day specimens or between the third- and fifth-day specimens.

Comment

Cutaneous-wound healing is associated with a new formation of connective tissue and epithelial regeneration. New collagen, which presumably furnishes the strength for wound healing, is thought to be brought about by two factors—elaboration of a protein material (probably from fibroblasts) and of a carbohydrate material, complex polysaccharides (produced by either mast cells or connective tissue cells[19]). Apparently the carbohydrate fraction is necessary for the protein component to develop into collagen. The elements of this dynamic repair process were studied by histochemical and histological methods. The complex

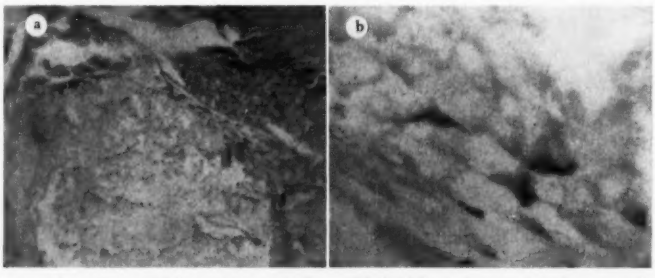


Fig. 8.—(*a*) Section of edge of wound showing periodic acid-Schiff-positive intracytoplasmic granules in new epithelial projection on fifth postoperative day. Alcian blue-periodic acid-Schiff stain; reduced approximately 45% from mag. × 100. (*b*) Oil-immersion view of periodic acid-Schiff-positive cytoplasmic granules in new epithelial cells on fifth postoperative day. Alcian blue-periodic acid-Schiff stain; reduced approximately 45% from mag. × 970.

carbohydrates were determined by the AB-PAS and toluidine blue stains; collagen and elastic tissue were identified by the orcein-Van Gieson method. Another factor associated with wound repair is reepithelization, which was studied by observing the length of the regenerating spur of epithelial cells, epithelial mitoses, and the cytoplasmic changes within the involved epithelium.

The increased presence of AB-PAS-positive material, presumably carbohydrates, on the third day within the dermis suggests that wound recovery had begun and was under way relatively early in the postinjury phase. This compares favorably with Dunphy and Udupa's observation concerning the healing of wounds in rats.[10] They noted either a very short or no lag phase, as described by other observers.[16]

On the fifth day it was observed that the staining reactions for complex carbohydrates within both the crust and the upper dermis had increased. The spinosum cells of the midepidermis at the edge of the wound were PAS-positive on the third day, and this reaction of the midspinosum layer was even more pronounced in the fifth-day specimens. This material is presumably glycogen. Lobitz and Holyoke have pointed out that this accumulation of glycogen is supposed to indicate recovery from injury and presumably is significant in the resulting regenerative process.[15] In the reepithelization process on the third and fifth days the midepidermal spinosum cells appear to be the most active cells in resurfacing the wound. More continuous observation might clarify this. Connective tissue healing progressed at the same rate of speed in all wounds and was impaired in none. No evidence of new elastic tissue regeneration was seen during the period under study.

It may be concluded that the solutions as used in this study exerted no apparent detrimental or beneficial influence on connective tissue wound healing, when compared to that of an untreated control.

Epithelization may be that phase of healing which can be retarded by compresses. On the third day there were noted no differences in reepithelization; but in four of six patients reepithelization on the fifth day appeared to be less advanced in all treated wounds when compared with the control. Under the conditions of this study there was no evidence of any clearly beneficial effect upon reepithelization from any of the solutions tested. It is apparent that the limited number of patients used restricts the value of these observations. Heifetz et al. have pointed out that certain surgical wounds may heal satisfactorily without benefit of customary surgical dressings.[17]

Summary and Conclusions

The effect of compress solutions upon aseptic wound repair in the human skin was studied by histologic and histochemical methods. Isotonic saline, distilled water, aluminum acetate (Burow's) solution, potassium permanganate, and urea comprised the tested agents.

A retardation of epithelization in the fifth-day specimens in wounds from four of six patients was observed in all treated lesions when compared to the untreated control.

No beneficial or detrimental effect of compresses upon connective tissue repair was detectable. No single solution tested appeared to be superior to any other solution or to the untreated control.

Even though epithelization may be retarded by wet dressings, as observed on the fifth day, eventual clinical healing was not delayed. These findings would not preclude the use of wet dressings upon infected lesions and for other dermatologic conditions where their usefulness is generally accepted.

The demonstration of polysaccharides and other carbohydrates on the third day again demonstrates the speed of initiation of wound recovery and shows that a lag phase, if one exists, must be short. All of the epithelial cells which were resurfacing the dermis beneath the crust had their cyto-

plasm filled with periodic acid-Schiff (PAS)-positive material.

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ABSTRACT OF DISCUSSION

DR. ROBERT G. CARNEY, Iowa City: Dr. Noojin's paper covers the subject beautifully and leaves me little to say about the mechanics of wound healing. It has long been my conviction that the skin heals at a more or less fixed rate under optimal conditions, these conditions being a healthy skin in a healthy person, the absence of pathogenic organisms, and freedom from irritating substances. Pending the discovery of an enzyme or hormone which actually stimulates orderly cell division, no topical or internal remedy is likey to reduce the healing time below that minimum achieved under these optimal conditions. Having lived through eras of cysteine hydrochloride, split leaf of aloe vera, chlorophyll, and red blood cell pastes, I was not surprised by Dr. Noojin's findings, in regard either to the lack of efficacy of the wet dressings under these conditions or to the fact that the untreated control possibly healed even faster.

As some of you know, we at Iowa have been very interested in the skin grafting of leg ulcers, one of the facets of the wound-healing problem. The reason for our entry into the field of skin grafting is interesting and has bearing on this paper. At that time, nearly 20 years ago, surgeons were preparing the wound or ulcer with strong disinfectants, trying to achieve a sterile field. Once two consecutive sterile cultures were obtained, pinch grafts were applied to this vitiated granulation tissue, along with petrolatum or cod liver oil. The graft was uncovered early, poked at to see if it was sticking, and often soaked with disinfectants. The results of such techniques were often appalling.

Our entry into this surgical field was simply to discover whether simple nonirritating techniques would not give better results. Once reasonably clean and healthy granulations were obtained through the use of simple wet dressings, the grafts were applied to the ulcer, dry dressed without greases or other foreign matter, and left strictly alone for five days. The results were vastly superior, and the only basic modification in this method has been the addition of an internal anti-infective agent for three days at the time of the graft to combat occasional mixed Staphylococcus and Streptococcus infections, which caused poor results in a small percentage of cases. Here, of course, we were not dealing with the clean aseptic wound, and Dr. Noojin has pointed out the usefulness of simple wet dressings under conditions of infection and inflammation.

All dermatologists know that irritants must be avoided in the treatment of dermatitis, and this same rule holds for the healing of wounds, clean or dirty. Dr. Noojin shows that even in a clean wound wet dressings do no harm, neither helping nor hindering the healing process. The healthy fibroblast and healthy epidermal cell have a fixed

schedule of repair that cannot be modified, at present, except for the worse. Dr. Noojin has scientifically proved and reemphasized the dermatologic maxim, "Do no harm."

DR. LEONARD F. WEBER, Chicago: The subject of wound healing is a daily problem in my practice. At least one-fourth of my industrial patients have a problem which is due to overtreatment of a simple or infected wound of the skin.

I should be interested in further studies regarding common antiseptics, as to how long they delay the healing of aseptic wounds in cases without overtreatment dermatitis. Not all patients become sensitized to thimersal (Merthiolate) or nitrofurazone (Furacin), although they are in first and second choice now.

The question of wet dressings has interested me a great deal for many years. Some years ago, and this goes back, probably, 25 years, I became interested in the complaint of some patients about aluminum acetate (Burow's) solution being uncomfortable and disagreeable. I did not agree with all of them. I discovered that if the aluminum acetate solution was colored with a few drops of methylrosaniline chloride (gentian violet), then it became agreeable to those who complained before it was uncolored. Nothing much was added, but it changed their mental outlook.

We are all interested in satisfying our patients. I agree with many of our patients that some local applications stink and stain and are objectionable from that standpoint. Recently, I have realized more than ever before that ointments, lotions, and wet dressings which, at least, are pleasing to the patient's eye will not aggravate his tension and ulcer. Industrial patients of the rough-and-ready type, particularly the men, prefer an ointment which is colored slightly, say orange or red, to one which is just white. Of course, men prefer red or yellow. Women prefer softer shades.

Color of the lotions, wet dressings, and internal medication makes a great deal of difference in the effectiveness of our treatment in those patients with many emotional outlets. Any of you who have not read "The Hidden Persuaders" will find it rather interesting reading. Certainly, the use of pleasing and agreeable local applications is not a new subject, but there is more to it than just what meets the eye.

DR. CHARLES C. DENNIE, Kansas City, Mo.: I am reporting three cases: Forty-five years ago, there came into the Massachusetts General Hospital a Greek with no scrotum. Both testes were bare. They were covered with pus and dirt. The surgical intern called me and said, "It's your case." I did not know what to do, so I used nothing but dry gauze as a dressing. The next day, the condition was improved. The dry dressings were continued for 10 days. Healthy granulations had formed by that time. Thiersch's grafts were placed upon these testicles. They all took, and the scrotal tissue that had crumbled up against the abdomen came down. A perfect result was secured. The pattern of the grafts looked like Grandma's crazy quilt. Both J. C. White and C. Morton Smith marveled at this job, especially the pattern of the scrotal tissue.

I told this to my commanding officer while I was going across to Europe, and he said, "That's interesting if it's true." We had two cases come in where they had stepped in a landmine, and, by some miracle, I do not know what, their scrotal tissue was blown off without injuring the testes. We followed the same procedure of dry dressings and skin grafts for 10 days, and so we got two perfect results. In my life, therefore, as a surgeon of this type, I have restored happily the scrotal tissue of three persons.

DR. HERMANN PINKUS, Monroe, Mich.: I like to refer to some experiments which Dr. Nicholas Gimbel of the Department of Surgery of Wayne State University did some years ago and in which I helped to interpret the results (Gimbel, N., et al.: A Study of Epithelization in Blistered Burns, *A. M. A. Arch. Surg.* 74:800-803 [May] 1957). The subjects were medical student volunteers. With the area under lidocaine (Xylocaine) hydrochloride anesthesia, burn blisters were produced by contact with the end of a weighted copper cylinder, 1 cm. in diameter, through which water from a thermostatically controlled bath vigorously recirculated. Some bullae were left undisturbed; some were aspirated, and others were unroofed. The burned areas were excised 5 to 14 days later for histologic study. Reepithelization was found to be fastest when the bullae were left intact. At the same time it was surprising for me to see the comeback power of the damaged dermal structures. At five days, most of the cells in the upper half of the corium appeared dead or degenerating. At the end of two weeks, hair follicles, glands, and blood vessels were repopulated from surviving deeper elements.

Another point on which I should like to comment is this question of which of the epithelial cells really migrate over the wound. Dr. Montgomery mentioned yesterday Dr. Hartwell's conclusions that the basal cells are relatively inactive and that the prickle cells seem to be the more active. I think that one can look at the situation in a different way. It has been well established by many workers that mitosis in the epidermis always occurs a few millimeters remote from the wound margin and that cells which are newly produced and also old cells become mobilized and cover the denuded surface by migration. The basal cells are apparently well fixed to the corium. They have a harder time to free themselves and to migrate,

so the higher cells, the prickle cells, at least those that are not fully keratinized as yet, begin to migrate earlier. But, really, the whole epidermis temporarily becomes an undifferentiated tissue. Or, as Argyris has said recently, there is modulation of various epithelial cells into an undifferentiated form. The events in wound reepithelization are another example that in the skin all the epithelia, even if they are already fairly far differentiated, can regress to an immature form and do almost anything that is required of them; that is, they may form new epidermis, both from old epidermis and from hair follicles. Possibly they even form new appendages.

DR. RUDOLF L. BAER, New York: The effects of wet dressings on cutaneous lesions must vary with different types of lesions. Most dermatologists use wet compresses for superficial acute or subacute and vesicular inflammatory processes and for subjective relief from itching, burning, and heat, rather than for wounds.

The effects of wet dressings on wounds to some extent depend on the depth of the wound. Dr. Noojin showed that in his wounds epithelization principally took place from the edge and not, as in the wounds cited by Dr. Pinkus, from the appendages at the bottom of the wound. Some years ago Dr. Sulzberger, Dr. A. Kanof, and I did some studies on healing and therapeutic effects on thermal burns. These were produced in a standardized manner with the Henriquez-Mortiz thermal burn apparatus in symmetrically situated sites on the arms and then treated on one side by one method and on the other side by a standard or control method (*Ann. Surg.* 125:418, 1947). Owing to the fact that the burns were quite deep, mostly third degree, there was slough formation which first had to be removed before the wounds could heal. In our studies it was shown that the therapeutic application of gels containing certain acids had a substantial influence on the speed with which debridement of the wound bed took place and, consequently, also on the time required for healing of the wounds which remained after removal of the slough. Weakly dissociated acids, e. g., pyruvic acid and phosphoric acid, appeared to be most efficient in this action.

The results of Dr. Noojin's work with various wet dressings are applicable to the particular type of wound which he produced and the therapeutic materials he employed. They should not lead one to condemn wet dressings in general as useless.

DR. LOUIS H. WINER, Beverly Hills, Calif.: R. Brett and O. Braun-Falco, (*Arch. Dermat. u. Syph.* 200:515-520, 1955) wrote that the periodic acid-Schiff stain was positive in the prickle cells of prickle-cell carcinoma and negative in the basal cells of basal-cell carcinoma. I observed Dr. Noojin's demonstration that the periodic acid-Schiff stain was positive in the regenerating epithelium, showing definitely that the prickle cells are active, as is the case in the proliferating cells of prickle-cell carcinoma.

DR. MARION B. SULZBERGER, New York: I should like to add just a few things to what Dr. Pinkus and Dr. Baer have said.

I should like to describe this burning apparatus, because it is such a useful tool. It was devised by F. C. Henriquez and A. F. Moritz, at that time at Harvard. It was designed for use during the war, to study the healing of thermal burns and wounds (Sulzberger, M. B.; Kanof, A., and Baer, R. L.: Studies on the Acid Debridement of Burns, *Ann. Surg.* 125:418 [April] 1947). This apparatus consists of a little metal cylinder which is filled with fluid, and around this cylinder there is an electric heating coil. The cylinder can never get appreciably warmer than the boiling point of the fluid it contains. So if one puts methyl alcohol in, one gets a lower temperature than if one puts in water, etc. This is a very ingenious way of determining the temperature of the burning contact. Then, there is a spring which presses the cylinder down through a guard, so that one can set the distance it projects and get a certain amount of pressure on the skin. And then, of course, one can vary the time during which one applies it, and so one can vary all the factors and always get a constant-sized burn, with constant predetermined and selected pressure and temperature for whatever period of exposure time one wishes.

Now, in studying these burns, in each subject two practically identical burns placed for paired comparison symmetrically on two arms, Dr. R. Baer, Dr. A. Kanof, and I had at our disposal very excellent ways for evaluating different methods of treating second- to third-degree thermal burns. The burns we produced were mostly third-degree burns. In those, one found two things.

One was that the only measure we discovered to make the treated burn heal more quickly than the control was to take out the necrotic tissue. That made a very appreciable difference, a statistically significant difference in healing time. Even infection did not make much difference in the rate of healing, in the long run. But *chemical debriding* did help, very substantially, in third-degree burns of this type.

The other point that our study showed was that in the depths of these wounds, when we took off the slough, we had a rather clean base. When we examined biopsy specimens of that base, there were no surface structures and no surface epithelium, but only rests of sebaceous and sweat glands; yet from these glands, islands of surface epithelium were generated, and finally the complete epidermal covering. This was our first evidence of what Dr. Pinkus has just said, namely,

that the glandular epithelium can regenerate into surface epithelium. I think that Lobitz has shown similar transformation in his experiments.

DR. RAY O. NOOJIN, Birmingham, Ala.: I should like to comment on three of the points that were raised. The abraded skin of rats has also been used to investigate the local effect on wound healing of a number of preparations (Randall, P., and Randall, R. J.: The Effects of Various Methods of Treatment on Wound Healing, *Plast. & Reconstruct. Surg.* 14:105, 1954). It was noteworthy that a number of preparations, including scarlet red ointment and Balsam of Peru, were irritating and interfered with wound healing. The rate of healing of the abraded skin apparently varies inversely as the degree of irritability of the substance applied.

As regards the regeneration of epithelial cells, we actually saw very few mitotic figures even though the tissue removed was fixed within two or three minutes after biopsy. As Dr. Pinkus and others have noted, these mitotic figures are usually found in the older epithelium some distance from the edge of the wound.

I agree with Dr. Baer's comments. We realize the limitations of an investigation of this type. On the other hand, it should be pointed out that all wounds, including the control, had the same opportunity to heal except for the solutions applied. Under no circumstances should my remarks imply that wet dressings are to be deplored for use in those conditions where their empiric usefulness is generally accepted.

Subcutaneous Filarial Infections

A Report of Two Additional Cases from Florida

WILEY M. SAMS, M.D., and J. WALTER BECK, Ph.D., Miami, Fla.

The filarial worms for which man is a normal host are not indigenous to the United States. Numerous other species of this family, however, are common parasites in fur-bearing animals of this country. Dogs, notably in this area and elsewhere in the coastal and Gulf States, are commonly infected with a heartworm, Dirofilaria immitis. This is an adult filarial worm which matures in the right heart and adjoining blood vessels. It is not to be confused with the very common intestinal parasites of the cat and dog, Ancylostoma braziliense and Ancylostoma caninum, and their larval stages, which produce the lesions of creeping eruption on the skin, so common to this area during wet periods.

A survey of the literature reveals a total of 37 cases of human infection with spurious filarial parasites of lower animals which have been recorded. Of the three cases reported in the United States, all were found in Florida, two from West Palm Beach [1,2] and the third in Jacksonville.[3] The following two cases are the first to be reported from the greater Miami area of infection with the spurious filaria of lower animals.

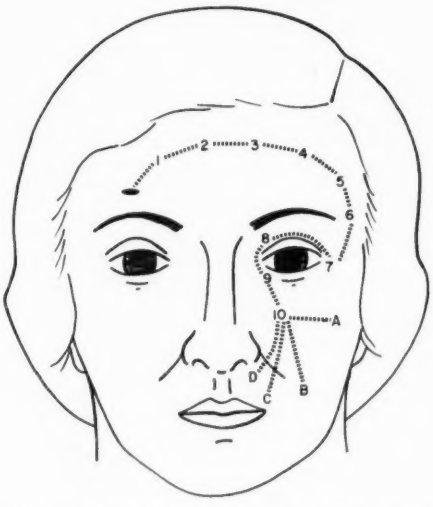

Fig. 1.—Course of filarial parasite described by patient in Case 1. The tendency to migrate in the loose tissue of the eyelids, about the conjunctivae, led to the original designation of this parasite as Dirofilaria conjunctivae when it appears in man. Though causing an inflammatory reaction, it leaves no clinical evidence of a residual track.

Report of Cases

CASE 1.—A housewife, aged 43, was seen May 9, 1957, with an inflammatory cystic lesion in the center of the left cheek. She believed her difficulty was due to a parasite which crawled under the skin, and she dated the onset of her trouble to a minor injury which she had sustained on the right side of her forehead. Subsequent to this event, she had made a trip to the Myakka River area on the west coast of Florida, and she believed that she had acquired her difficulty either on this trip or from the injury which had previously occurred. In any event, she developed a migrating lesion on the forehead which produced at times a crawling, tingling, or itching sensation. After several days, the upper left eyelid became swollen near the outer canthus. It was inflamed, and she felt a "gnawing" sensation. She claimed the "eye became red and inflamed, and the eyelid puffy." After a time this process localized near the edge of the upper lid at the outer canthus, and it appeared as if a sty were forming. Later, the swelling appeared on the lower lid near the lacrimal papilla, and itching, inflammation, and swelling occurred in this region. Again, the symptoms were described as "gnawing" and disconcerting, with a fiery

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University of Miami School of Medicine; Clinical Professor of Dermatology, Department of Medicine (Dr. Sams), and Associate Professor, Department of Bacteriology (Dr. Beck).

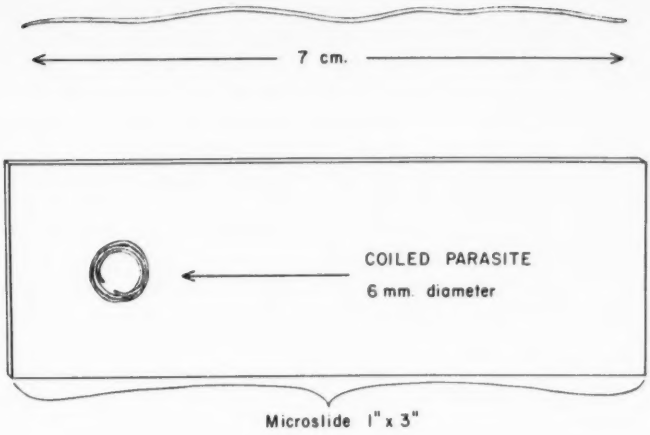

Fig. 2.—Diagrammatic representation of coiled parasite to illustrate size in comparison with a microscope slide. Parasite measured 0.25 mm. in diameter and 7 cm. in length.

stinging sensation that prevented sleep at times. As swelling and induration increased in the area, she consulted several physicians with a story of having a "parasite." She saw an internist, a second physician who had an office in her neighborhood, and a dermatologist, but none of them considered the condition she presented could be the result of a parasite, nor was there a residual track of a migrating inflammatory reaction. At the time of examination the lesion was sharply localized in the center of the left check and the skin appeared to be under tension, as if there were a localized area of purulent exudate (Fig. 1). Although transient areas of swelling had occurred on the lip and check, there was no residual evidence here of inflammatory reaction. Since she had the scars of many cystic lesions from an old acneiform eruption, this was accepted as a lesion of similar character with secondary infection. A small incision was made in the center of the inflamed nodule, and slight pressure was applied. No pus or sebaceous material was discharged, but a clear gelatinous exudate, containing a small, coiled, pink, translucent, thread-like body appeared. This was placed on a slide in a drop of tap water (Fig. 2). As the coil was teased apart, athetoid movement was noted, and a thread-like organism in two parts was present for examination. Under the low-power objective, fine horizontal cuticular striations could be seen, as well as a central alimentary canal and what appeared to be an opening near the sharply pointed end of the longer segment. Subsequent examination disclosed a filariform parasite which measured 0.24 mm. in diameter and was approximately 7 cm. in length. The structure of the organism was that of the immature female filariform worm, D. immitis. The lesion described, and all symptoms, promptly disappeared after removal of the parasite.

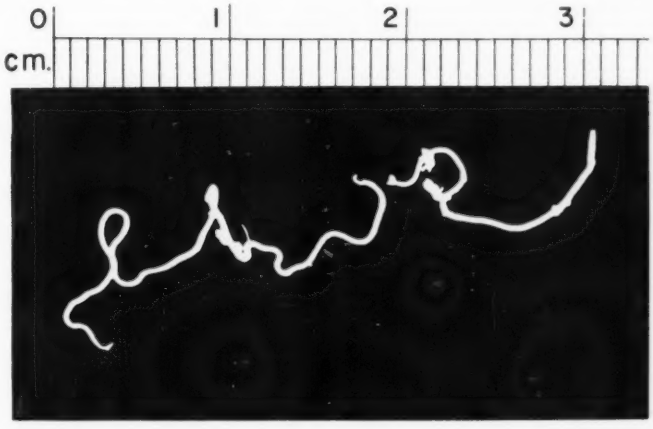

Fig. 3.—Photomicrograph of dirofilarial parasite taken after preservation.

CASE 2.—A woman, approximately 60 years old, consulted her physician * because of a lump in her left breast. Clinically, he felt the appearance suggested fat necrosis, or perhaps a scirrhous type of carcinoma. When excised and submitted for pathologic examination, it apparently showed a granulomatous type of tissue; it was reported as an inflammatory reaction (July, 1956). At a later date, she developed a rubbery-like tumor of nodular character on the right forearm. This lesion was excised and submitted for histologic examination and was found to contain a parasite, with many cross sections of the organism in the sections examined. A subsequent review of the inflammatory lesion from the breast revealed a parasite of similar character. These sections were subsequently reviewed by parasitologists, who felt that the parasite was a filarial worm but were unable to identify the organism in the sectioned material. In reviewing the history with this patient, a crawling, tingling, gnawing sensation was reported as having occurred in the lesion on the forearm, but it had not been noticed in the lesion on the breast.

Comment

All infections from Florida, including the two cases here reported, are those of parasites identified as Dirofilaria conjunctivae. This species was established by Desportes in 1939-1940 for immature female filariae recovered from man and regarded as identical to the worm described by Addario in 1885. Since no mature males have been recovered as yet, species identification is not possible at this time. The designation D. conjunctivae has been temporarily selected for convenience, since a number of parasites have been recovered from the eyelid or tissues adjacent to the eye.

It is of interest to note that the heartworm of dogs, Dirofilaria immitis, is mosquito-borne. In view of the fact that humans in this area are bitten repeatedly by the same mosquitoes, the thought naturally arises that possibly the human infection reported here is that of D. immitis. It has been suggested by Faust [1] that D. conjunctivae may be D. immitis in an abnormal host. In 1956, Newton and Wright [3] reported for the first time in the United States another filarial worm in dogs. The adult parasite was found in the subcutaneous tissue of the host, and the microfilaria produced were morphologically different from those due to heartworms. Since D. conjunctivae in man is found in the skin and subcutaneous tissue and the new filarial parasite of dogs is likewise subcutaneous in habitat, one is led to suspect that D. conjunctivae may possibly be synonymous with this parasite. The new filarial worm in dogs had been tentatively classified in the genus Dipetalonema, and the chief intermediate host, experimentally at least, appears to be the dog flea. Thus another parasite must be considered as the possible species found in man and another vector suspected as a source of this rather unusual parasitic infection.

For physicians in Florida in particular, and those elsewhere in the United States, the significant point to date is the appearance of five cases involving the skin and subcutaneous tissue in which the spurious filariae of lower animals has been recovered. One might rightly surmise that other cases have occurred and passed undiagnosed to terminate spontaneously. It is hoped that physicians, especially those in Florida, or those who see patients from Florida, will bear in mind this possibility, and excise, or carefully open, suspicious cysts and avoid the destruction of parasites which may be present. Parasitic material of this type is best held at icebox temperature pending fixation and adequate examination.

Examination of the blood in Case 1 did not reveal microfilariae. They are readily demonstrated in the blood of dogs who harbor fully matured parasites of either species. When microfilariae are present, a proper identification of the parasite may be made. In such cases an attempt should be made to infect a suitable arthropod host in order to complete the life cycle. In this manner additional light may be cast on this as yet unsolved parasitic disease in man.

Summary

Two additional cases of infection caused by Dirofilaria conjunctivae are reported.

* Reported with permission of Dr. Ferdinand Kauders, Miami, Fla.

This brings to five the number of cases reported from this country, all from Florida. Suggestions for further investigation and study are made for physicians who may observe additional filarial infections of this type.

308 Ingraham Building (32).

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ABSTRACT OF DISCUSSION

DR. WILLIAM L. DOBES, Atlanta: These case reports are most interesting.

Filariasis is an infection with one or more of several true filarial worms. Filarial worms are characteristically thread-like in appearance. Probably, the best known filarial infection is elephantiasis, produced by Wuchereria bancrofti. Infected mosquitoes introduce the larva into the skin, and the microfilariae are later found in the viscera and the peripheral circulation, where they produce lymphatic obstruction.

In certain parts of Africa and Asia, ingestion of water polluted with the Guinea worm may cause dracontiasis. Adult worms develop within the host. Later, the viviparous female makes her appearance, laden with larvae, in a pea-sized itchy indurated lesion which is usually or frequently on the foot or leg.

In equatorial Africa, the mango fly infects the skin with Loa loa, producing loaiasis. This filaria inhabits the subcutaneous tissues, persistently migrating a few centimeters a day in a raised serpentine track. It has a tendency to wander across the cornea and is thus often called the "eyeworm."

The filariasis that resembles Dr. Sams' cases most closely is onchocerciasis, which is transmitted by the biting gnat, Simulium. It is found in Africa, as well as in Guatemala and in southern Mexico. The adult worms live tightly coiled in fibrous subcutaneous tumors, varying in size from that of a pea to that of a small orange. The unsheathed microfilariae escape from the parent tumor and migrate through the skin and subcutaneous tissues, often involving the corneal conjunctiva.

The original case, reported from West Palm Beach, was in a 19-year-old girl. The upper eyelid showed a reddish-gray nodule, firm but rubbery, with a coiled thread-like worm about 50 mm. in length.

Another case reported from Jacksonville was that of a 35-year-old woman who had a small lump on her arm. Incision over the site of the lesion revealed an actively motile female filaria.

Microscopically, both cases were examples of infection with Dirofilaria conjunctivae.

There are several interesting features about the cases reported by Dr. Sams. The previously reported cases from Florida were those of encysted subcutaneous nodules. In addition, the first case of Dr. Sams developed a migrating lesion, and the parasite was finally removed from a tumor. The migration was very similar to that of the microfilaria of onchocerciasis.

In Case 2, the first lesion was present in the left breast, and, at a later date, another filarial tumor developed on the right forearm. A tingling, crawling, gnawing sensation was felt, but actual migration did not take place. The two lesions occurred after an interval which suggested a greater likelihood of transfer from a flea, which is more likely to remain in the vicinity, than from a mosquito.

There are a few conflicting reports on the ability of Dirofilaria to develop in fleas. One can, however, find in the literature sufficient basis to suspect that there may be more than one dog filaria in this country. One should also note that the species Dirofilaria is a common cause of filaria in dogs over the entire United States. If the species has caused five reported cases in Florida, why have not similar cases been reported in other states?

Whatever the case may be, the human apparently is not an appropriate host and is physically resistant and unadapted to allow penetration of animal filaria into the cutaneous blood vessels. In only two instances of human infection has Dirofilaria been reported internally: Once, a single worm was found in the left ventricle in Brazil and once, in the inferior vena cava in Louisiana.

The first case of Dr. Sams also demonstrated that the patient's history often may be more important and more helpful in arriving at a correct diagnosis than a narration of a seemingly neurotic person would indicate. Case reports such as these are stimulating and come to remind us of the constant need for alertness and investigative reasoning.

DR. V. PARDO-CASTELLO, Havana, Cuba: When I was consulted about this condition, I must say that I was much surprised. I had never heard of it. Nevertheless, I went to the Department of Parasitology of the University of Havana, and

I was told that they had never seen a case in a human being but that they had seen two beautiful specimens in dogs. These dogs were from the rural sections of Cuba. Their owners, who prized them highly, went to the veterinarian and wanted to know if an autopsy could be performed to determine the cause of death. This was done, and it was found that the hearts of those dogs (one of which you saw here) were full of these filaria.

The classification of this parasite was done by the professor of parasitology of the University of Havana, and it was called Dirofilaria immitis. The condition has not been found in the human being in Cuba. All my colleagues whom I consulted were absolutely ignorant of the presence of such a condition in the human being.

Naturally, we may have passed over some cases because we were not prepared, or we did not know of the existence of such a condition. Perhaps, in the future, the suspicion having been aroused in us, we shall be able to contribute to such findings.

Dr. Donald M. Pillsbury, Philadelphia: A couple of years ago, in Africa, I had the opportunity of seeing rather a large number of cases of onchocerciasis. I do not know what the relationship of that particular filaria is to the one that Dr. Sams reported, but it is remarkable, in these cases, to see the lack of inflammatory reaction which is produced by the parasite. Also, in onchocerciasis, as you know, some of the lesions will be nodular but in other areas where microfilariae invade the skin, the skin looks perfectly normal; yet, if one does a scraping, as for the Mycobacterium leprae bacillus, one obtains many organisms from what seems to be entirely normal skin.

It is also a curious fact that in Africa, although the disease is very common, it is only in certain geographical areas that the conjunctiva becomes involved.

Dr. Thomas B. Fitzpatrick, Portland, Ore.: A few months ago we saw a 35-year-old male physician with a presenting complaint of pruritus of the lower extremities. The eruption was not extensive and involved scattered areas on the lower legs and dorsum of the feet and consisted of tiny purpuric macules. The lesions were suggestive of one of the dermatologic purpuras, such as Schamberg's disease. There were two unusual features, however; the patient had just returned from three months in Central Africa, and on careful questioning it was discovered that the purpuric lesions were periodic in their appearance, occurring in showers. We were able to demonstrate the microfilariae of Wuchereria bancrofti in direct smears obtained by scraping the lesions.

In this era of international travel, we must be constantly aware of tropical diseases, and in attempting to diagnose bizarre lesions, we should obtain a recent travel history.

Dr. Wiley M. Sams, Miami, Fla.: I believe the subject of parasitology will have to be enlarged because, just as Dr. Fitzpatrick has said, the world is growing smaller.

Immunologic Aspects of Herpes Simplex, Herpes Zoster, and Vaccinia

G. DOUGLAS BALDRIDGE, M.D., Beverly Hills, Calif.

The objective of this paper is to present data regarding the immunology of three cutaneous viral diseases. These data will be used as the basis for a brief discussion of certain methods of treatment of these diseases.

Herpes Simplex

A proper concept of the host-parasite relationship in herpes simplex infections is basic to an understanding of the immunology of this disease. The virus makes its original invasion between the ages of 1 and 5 years in a majority of persons. The usual manifestation at this time is a subclinical gingivostomatitis. Occasionally, the local symptoms are severe and require medical attention. Rarely, the virus invades the inflamed skin of a patient with a preexisting dermatitis. This latter syndrome is called eczema herpeticum. Because of the massive nature of the onslaught, toxic symptoms are more pronounced.

After this initial penetration, the virus goes into a latent state in a localized area of the skin, where it remains for the lifetime of the patient. The commonest sites of localization are the lips, penis, and buttocks. While in this quiescent phase, the virus in-

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From the Department of Dermatology, University of Southern California School of Medicine, (M. E. Obermayer, Professor), Los Angeles, and The Beverly Hills Medical Clinic.

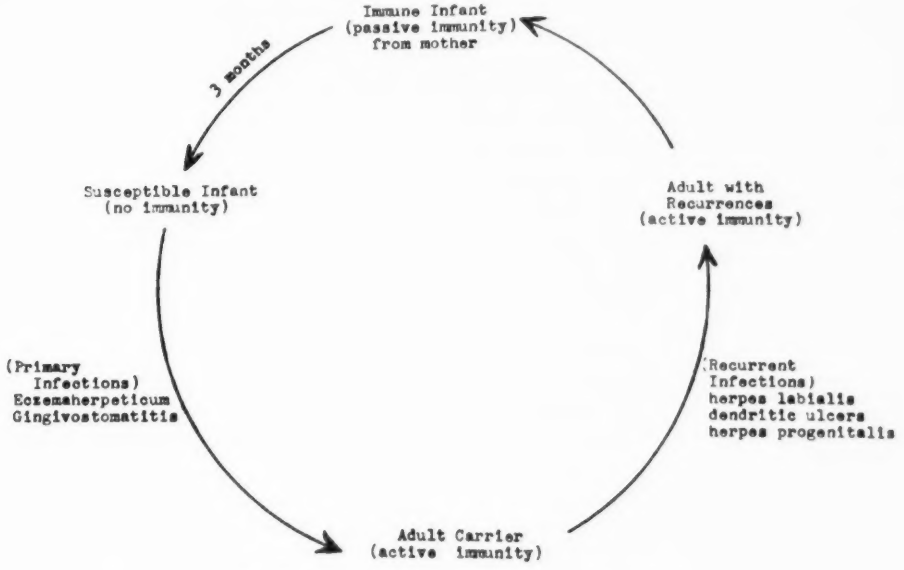

Fig. 1.—Patterns of immunity in herpes simplex.

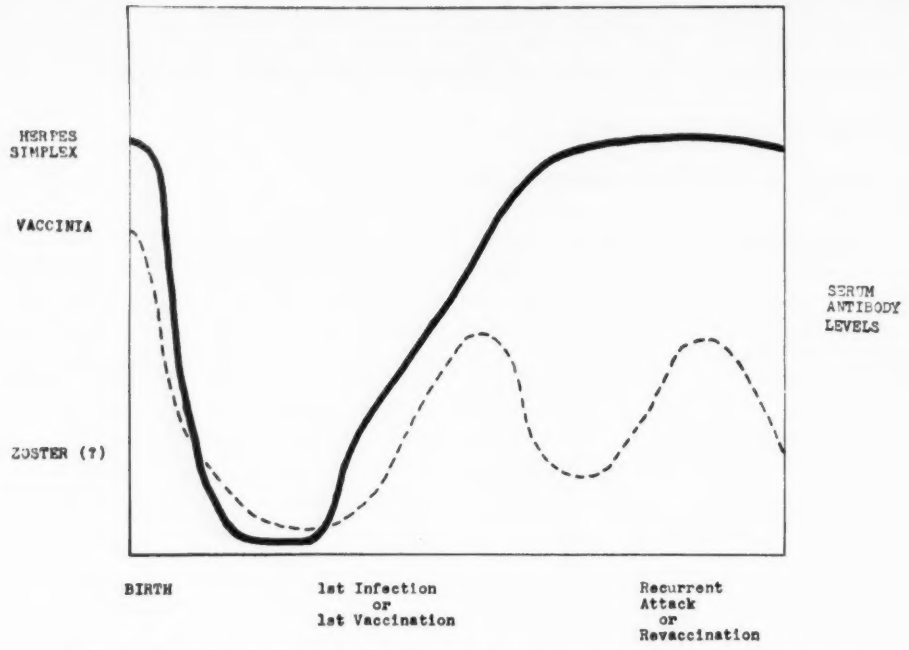

Fig. 2.—Expected serum antibody level alterations in patients with herpes simplex and vaccinia.

duces no noticeable symptoms. Occasionally, however, the virus "awakens" from its dormancy and attacks the surrounding tissues, producing redness, swelling, and vesiculation. These symptoms last only a few days. The virus then returns to its resting stage, only to be reactivated periodically. These recurrent manifestations can be "triggered" by many factors, such as fever, exposure to sunlight, and emotional stress. Herpes virus is recoverable from the lesions of both the primary and recurrent phases of the disease.

Unique immunologic changes take place during the development of the relationship between the host and parasite. At birth the infant possesses a temporary immunity as a result of passive transfer of antibodies through the placenta. This antibody titer falls to zero within a few months. The child is now unprotected. When primary invasion occurs, active antibody manufacture begins and the serum virus neutralizing antibody rises to a high level within two weeks. Except for occasional moderate spontaneous fluctuations, this high antibody titer remains constant for life. This virus-neutralizing antibody inactivates the virus on direct contact. This is demonstrated by the fact that if serum drawn from patients having a history of herpes is allowed to contact known live herpes virus, subsequent injection of the mixture into a susceptible laboratory animal will produce no disease.

Recent experiments by Geller et al. have demonstrated the in vivo effectiveness of neutralizing antibody.[1] These authors have confirmed the fact that, during the primary attack, the virus may be recovered from the blood stream of the patient. Later, as the neutralizing antibody levels rise, recovery of the virus becomes increasingly more difficult. In another study they injected live herpes virus into human volunteers, all of whom possessed neutralizing antibodies. Blood samples removed from the opposite arm of the patient, during and

after the injection, failed to yield significant amounts of virus.

From an immunologic standpoint, the important feature is the fact that, unlike most other infectious diseases, the presence of circulating antibodies, "lethal" to the virus itself, is no guarantee of immunity from recurrent outbreaks. As a corollary, there is no increase in neutralizing antibody titer during or after a recurrent attack of herpes.

Although one thinks of the immunology of herpes as being unique, it is interesting to note an observation made in 1936, by Wise and Sulzberger: "It is to be recalled that circulating antisubstances by no means necessarily confer skin immunity even when present in high titer. This can be seen, for example, in some cases of furunculosis persisting despite high blood staphylococcus antitoxin titers." [2]

Although recurrent herpes is seldom more than a minor annoyance to the patient, the large numbers of persons affected and the occasional severe case make control of this disease important to the dermatologist.

Smallpox Vaccination.—By far the commonest method of treatment of recurrent herpes is repeated inoculations of ordinary smallpox vaccine. This technique resulted from a report by Gildermeister and Herzberg, in 1925.[3] They claimed to have produced a relative immunity of the rabbit cornea to vaccinia by prior inoculation with the virus of "febrile herpes." They concluded that there was a definite immunologic relationship between these two viruses. This view was soon challenged by Bedson and Bland.[4] In a well-controlled experiment they titrated the infectivity of vaccinia in herpes-immune guinea pigs, performed the reverse, and finally executed cross neutralization experiments with both viruses. They concluded that herpes simplex and vaccinia are totally unrelated. This is the accepted view of immunologists and virologists today.

The foregoing evidence might lead the critical physician to conclude that smallpox vaccination can be of no value in the management of recurrent herpes. The overwhelming experience of most dermatologists, however, indicates that this method of treatment is effective in reducing the incidence of outbreaks. For example, a recent paper by Schiff and Kern describes complete remission in 52 out of 68 cases of recurrent herpes following smallpox vaccination.[5] In an unpublished study, the same authors have observed a much higher incidence of remission in a smallpox-vaccinated group as compared to a control group inoculated with heat-killed vaccine.[6] How can one account for this apparent beneficial effect? It seems unlikely that simple spontaneous remission could be responsible for the results obtained. Many observers, including myself, believe that this effect is due to suggestion. There is support for this view. Blank and Brody have demonstrated that herpetic recurrences can be prevented by psychotherapy alone.[7] A recent study by Rasmussen et al. indicates that mice placed under emotional stress are more susceptible to infection with herpes than are those in a control group.[8] The well-recognized etiologic relationship between human emotional stress and herpetic recurrences may be construed as further support for this concept. Lastly, the curative effects of suggestive procedures in viral infections has a precedent in the case of warts in which psychotherapy is also effective.

Vaccination with Inactivated Herpes Virus.—Injections of formolized herpes virus produce some degree of immunity in animals.[9] The same approach has been attempted in humans. Unfortunately, in man such injections produce neither an increase in antibody titer nor do they cause clinical remission.

Vaccination with Active Herpes Virus.—This method has been used sporadically by several physicians. The results are best summed up in the recent conclusions of Lazar, who stated, "Two instances of homovaccination using unmodified material taken from the sites of recurrent herpes simplex

infection are reported. In both cases a second site of recurrent herpes simplex was initiated. No benefit followed this approach." [10]

Herpes Zoster

In order to collect data pertaining to the nature of neutralizing substances in humans with a viral infection, laboratory animals susceptible to that particular disease are essential. There is no animal other than man susceptible to zoster. As a result, knowledge of the immunology of this condition is rudimentary. Recent experimental work with human tissue cultures are interesting but are not yet of practical value. Because of the rarity of recurrent zoster, it is safe to infer that immunity of some sort develops during the course of the disease. The demonstrated specific agglutination of zoster elementary bodies by convalescent zoster or varicella serum also indicates that there is an immunologic response in zoster patients.[11] Some attempts at immunotherapy have been made during recent years. These have been confined to injections of γ-globulin or convalescent serum during the course of the illness. Beneficial results have been claimed for this method of treatment, but these claims have been based on uncontrolled clinical studies only.[12] Experience with other viral diseases indicates that by the time the symptoms appear the virus has reached the intracellular position and is not susceptible to circulatory immune substances because of the impermeability of cell walls to antibodies. A recent study by the Burgoons' and Baldridge showed that the occasional spectacular case of zoster has unfavorably colored the clinical picture of this illness in the minds of many clinicians and that zoster is a much more benign disease than was heretofore realized.[13] It may well be that the patients for whom beneficial results were claimed by immunotherapy were merely following the natural course of the disease. A well-controlled clinical investigation should settle this matter.

Vaccinia

In contrast to zoster, the immunology of vaccinia has been explored very thoroughly, probably more than any other viral disease. The effectiveness of vaccination in the prevention of smallpox and vaccinia has been recognized since the time of Jenner. The solid immunity produced by vaccination is due to the development of circulating serum virus-neutralizing antibodies. These antibodies reach a potent level within two weeks after vaccination. They remain at an effective titer for three years or more. Other types of antibodies, such as complement-fixing, also develop, but these are of less importance to the clinician.

Of the numerous cutaneous manifestations of human vaccinia, I shall discuss only three: eczema vaccinatum, generalized vaccinia, and progressive vaccinia.

Eczema Vaccinatum.—Eczema vaccinatum follows the inoculation of vaccinia virus into the broken skin of a person with a preexisting skin disorder, such as atopic dermatitis. If this person is deficient in specific neutralizing atibodies, the virus is able to propagate rapidly and establish multiple sites of infection on the skin surface. Whether this spread is hematogenous or via the skin surface has not been determined. Once the disease begins, the prognosis for the patient depends on his ability to form neutralizing antibodies. In most untreated cases, antibody formation begins promptly after the infection is initiated and regression of the lesions begins after about one week. Some patients, however, are slow or unable to form antibodies and may be overwhelmed by the virus. In such patients, the early injection of specific vaccinial immune globulin may be of benefit.[14] This material is prepared from blood collected from donors who have been successfully vaccinated against smallpox four to eight weeks prior to donation.* Cases of accidental inoculation of vaccinia in vital areas, such as the cornea, should be given specific

* Available from Dr. Henry C. Kempe, University of Colorado Medical Center, Denver.

immune serum for protection. Generalized vaccinia is similar in all ways to eczema vaccination, except that the spread is probably hematogenous. Again, if given early enough, specific immune globulin may be effective.

Progressive Vaccinia.—This is a rare complication of ordinary smallpox vaccination. It is characterized by steady enlargement of the vaccination site and the formation of progressive satellite lesions. It is usually seen in patients who have a defect in γ-globulin formation.

In cases of agammaglobulinemia the disease is routinely fatal despite any method of treatment. If, on the other hand, the γ-globulin produced by the patient is defective, (dysgammaglobulinemia) specific immune therapy may be of value.[15]

It is of interest that most children with agammaglobulinemia go through the smallpox vaccination procedure without abnormal manifestations. This is possibly explained by the presence of immune systems independent of γ-globulin, which have been described recently.[16]

Summary

The immunologic responses of humans infected with herpes are unique. Human serum containing these antibodies protects susceptible experimental animals from infection. The presence of circulating antibodies in the blood stream of the patient confers no protection against recurrent attacks of herpes. Recurrent herpetic attacks do not stimulate antibody production as does the initial invasion.

Present methods of treatment involve attempts to raise neutralizing antibody titers. None of the methods employed have accomplished this objective. Even if antibody production could be increased, this would be of no value because those patients afflicted with recurrent herpes routinely possess a very high level of circulating virus-neutralizing antibodies.

There are two practical approaches to the control of recurrent herpes. The first is the avoidance of trigger factors, such as exposure to sunlight. The second is the use of repeated smallpox vaccination. The reason for the success of this type of therapy is, as yet, undetermined. It is probably a result of psychological suggestion, analogous to the results obtained by suggestive procedures in wart therapy.

Immunotherapy of zoster with γ-globulin and convalescent serum has been tried in an occasional case. Judging from the evidence presently available, it is doubtful if such therapy influences the course of this disease.

Specific immune globulin is available for the prevention and treatment of human vaccinia. This material should be effective if given before the onset of symptoms. Its efficacy as a form of therapy has yet to be proved.

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Gamma-Globulin Therapy in Chronic Staphylococcic Dermatoses

A Comparison of Serum Gamma-Globulin Levels and Serum Antibacterial Activity

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Bruton [1] reported that decreased serum γ-globulin may accompany susceptibility to infection. It is, therefore, important to consider dysgammaglobulinemia, hypogammaglobulinemia, and agammaglobulinemia in patients presenting acute and chronic infectious dermatoses. γ-Globulin serum levels have been extensively documented for many dermatologic entities, generally representing the acute infectious and severe varieties. The chronic dermatoses, in which staphylococcic diathesis is an important feature, have received less attention.

The purpose of this study is to (1) determine whether the sera of patients with chronic staphylococcic dermatoses have a lowered antibacterial titer, (2) to determine whether the serum γ-globulin levels are reduced, and (3) to observe the response of these dermatoses to γ-globulin therapy.

Investigational Methods

Three general methods were used during this investigation.

A. Clinical Classification of Chronic Staphylococcic Dermatoses and Response to γ-Globulin Therapy.—The chronic staphylococcic dermatoses are divided into diagnostic groups for a more accurate presentation of the dermatosis under consideration. Of necessity, these groups are not too arbitrary but represent common clinical divisions of chronic staphylococcic dermatoses.

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I. Staphylococcic Eczematoid Dermatitis: Staphylococcic eczematoid dermatitis is usually presented with a history of cradle cap with extension of the dermatitis to involve the ears, occiput, neck, cubital and popliteal fossae, and diaper region, sometimes becoming generalized, persisting to age 2 to 3 years, and then regressing. There is no association with diet or environmental sensitivities. The dermatitis recurs at early puberty, usually between the ages 9 to 12 years, to involve the scalp, back and sides of the neck, face, cubital and popliteal spaces, pubis, and external genitalia and may be generalized. It is characteristically dry, scaling, infiltrative, and pruritic and is associated with folliculitis. It is generally worse during the winter months and regresses during the summer months. The patient is nervously tense, but this is probably secondary to the dermatitis, as nervousness regresses as the dermatitis improves. Diet has no effect on the dermatitis, although some patients present concomitant allergies.

II. Seborrheic Dermatitis: Seborrheic dermatitis typically involves the scalp and occiput, with extension out of the scalp line onto the forehead, neck, external ear canals, eyebrows, nasolabial folds, axillae, chest, umbilicus, and pubis.

III. Intertrigo: Intertrigo occurs on the skin folds beneath the breasts, axillae, crural region, and natal cleft and usually shows peripheral folliculitis.

IV. Pyoderma: Pyoderma, as encountered in this study, most commonly occurred on the dorsal surfaces of the toes, feet, fingers, and hands. It usually persisted from onset at age 1 to 2 years to young adulthood. There is no evidence of fungus infection or venenata.

V. Folliculitis and Furunculosis: The variety of folliculitis and furunculosis considered for this study is chronic, persisting over a period of months and years.

VI. Acne Vulgaris: Acne vulgaris is of the severe type, involving the face, chest, shoulders, back and deltoids, not necessarily cystic, but showing a marked tendency to folliculitis and pustules.

B. Serum Electrophoresis.—Serum electrophoresis was carried out in the Spinco Model R paper-

TABLE 1.—*Patient γ-Globulin Determinations, Diagnostic Groups, and Clinical Severity*

Total Patients, No.	γ-Globulin Deviation from Normal, %		Diagnostic Groups						Clinical Severity		
			I	II	III	IV	V	VI	Mild	Moderate	Severe
1	Plus	76:100	1								1
5	Plus	51:75	5								1
10	Plus	26:50	5	2		3				7	11
22	Plus	1:25	7	4	1	6	1	3	1	12	9
32	Normal	0	12	6	3	9	1	1	3	16	12
41	Minus	1:25	16	1	3	13	3	5	1	19	13
38	Minus	26:50	21	2	4	1	9	1		25	26
17	Minus	51:75	4	1			2	10		5	5
4	Minus	76:100	3				1			3	
—			—	—	—	—	—	—	—	—	—
170			74	16	11	32	17	20	5	87	78

strip-electrophoresis apparatus. The separated patterns were stained in bromphenol blue, and the percentage of serum components were calculated from the RB Analytrol integration curve. Control values were determined from runs on normal persons.

C. Serum Antibacterial Activity.—The technique described by Wood, Ono, and Bessey[2] was used to determine the total serum antibacterial and properdin levels.

Gamma-Globulin Determinations

γ-Globulin determinations were made on 170 patients. It can be seen from Table 1 that 32 patients (19%) showed normal γ-globulin readings, 38 patients (22%) deviated above normal, and 100 patients (59%) were below normal.

With reference to the diagnostic groups, 60% of the patients with staphylococcic eczematoid dermatitis showed decreased γ-globulin, 24% of the patients with seborrheic dermatitis showed a decrease, as did 63% of the patients with intertrigo, 44% with pyoderma, 82% with folliculitis and furunculosis, and 85% with the pustular type of acne vulgaris. Folliculitis, furunculosis, and pustular type of acne vulgaris may represent a severer type of bacterial infection. γ-Globulin levels are not diagnostic for these entities, but low γ-globulin readings may be anticipated, and the performance of protein electrophoresis is justified.

The clinical severity of the dermatoses presented by these 170 patients was considered mild for 5 patients (3%), moderate for 87 patients (51%), and severe for 78 patients (46%). The moderate group showed 19% γ-globulin readings of normal; 21%, above normal, and 60%, below normal. The severe group was 15% normal, 28% above normal, and 57% below normal. While the γ-globulin levels did not exactly correlate with the severity of the disease process, there was a definite tendency for the severer types to show below-normal readings. Low γ-globulin titer may be a factor in increased severity.

No correlation was made in this study between γ-globulin levels and the ages of the patients. However, it is recognized that there is a normal γ-globulin level in the newborn infant due to passive donation from the mother, a temporary lowering at about 4 months of age, and a gradual rise to normal by 1 year, as reported by Barrett and Volwiler,[3] and between 2 and 6 years, as reported by Mazzitello and Good.[4] This might explain the occurrence of staphylococcic eczematoid dermatitis in young children, its regression during older children, and its recurrence at early adulthood due to possible onset of acquired hypogammaglobulinemia. Key and Nelson[5] suggest that Leiner's and Ritter's diseases and impetigo neonatorum may be associated with hypogammaglobulinemia.

Antibacterial Activity of Serum

The method used to determine serum antibacterial activity measures two general groups of substances found in serum: (*a*)

the total antibacterial activity and (*b*) those components of serum which require complement for activity and are destroyed by heating the serum at 56 C for 30 minutes.

From Table 2, it can be seen that of the 61 patients on whom comparison studies were made between γ-globulin determinations and total antibacterial activity nearly all the patients had a reduced γ-globulin reading and about 70% had lowered total serum antibacterial activity. The relationship between lowered γ-globulin and reduced serum antibacterial activity was most remarkable. It should not be assumed, however, that there is a direct relationship between γ-globulin and serum antibacterial titers. Though both components play an important role in protective mechanisms, they vary independently. It has been reported elsewhere[6,7] that patients with normal γ-globulin levels are capable of extremely high antibacterial titers when under the stress of acute infections.

There are many components of normal human serum which inhibit bacterial growth.[8] However, those reported here are divided into the two general groups described previously. Table 2 shows a breakdown of serum antibacterial titers for these two major groups. The center of the Table compares the units of total antibacterial activity measured for 61 patients. It can be seen that only 24.5% gave normal titers. It should be pointed out that three of the patients examined gave no measurable antibacterial activity. All of these three patients had severe dermatoses and showed excellent response to therapy.

In comparison, the right side of Table 2 shows the units of activity represented by those factors in serum which require complement for activity. Of the 61 patients examined, 55.7% of them were normal. Eleven of these patients gave no complement-depending antibacterial activity. The majority of patients deficient in the complement-depending factors were extremely lower than normal, that is, less than 0.5 units. Inasmuch as properdin is probably the major component of this group, its absence in these patients appears to be of great significance. It was of particular interest that no patients either in the control group or with infection showed an increase in antibacterial titer. An increase in serum antibacterial activity is related primarily to acute infection[6,7] and would support these findings, inasmuch as our patients were all of the chronic type.

TABLE 2.—*Comparison Below Normal γ-Globulin Determinations with Total Serum Antibacterial Activity and Complement-Depending (Properdin) Activity*

γ-Globulin			Total Antibacterial Activity		Complement-Depending Activity	
Patients, No.	Below Normal Deviation, %		Patients, No.	Range,* Units (8.5±1.7)	Patients, No.	Range,* Units (2.5±1.01)
2	Minus	100:76	4	0-1	23	0. -0.5
6	Minus	75:51	3	1-2	3	0.6-1.0
18	Minus	50:26	4	2-3	1	1.1-1.5
25	Minus	25: 1	11	3-4	34	1.6-3.5
10	Normal	0	14	4-5		
			10	5-6		
			15	6-10		
—			—		—	
61			61		61	

* Standard deviation from mean calculated from 24 healthy normal humans.

Gamma-Globulin Therapy

While γ-globulin therapy has been reported by many authors to be of benefit in the management of acute, recurrent infections, a review of the literature did not disclose its extensive use, heretofore, for chronic dermatoses presenting associated staphylococcic infection. We are indebted to the American National Red Cross for ample supplies of poliomyelitis immune globulin (human), identical with immune serum globulin (human).

Recommended dosage for maintaining levels adequate to combat hypogammaglobulinemia is 0.3 ml. per pound of body weight, administered at monthly intervals.[3] However, for practical purposes, 6 ml. for infants, 10 ml. for young children, and 20 ml. for adults was injected intragluteally at from three- to four-week intervals.

TABLE 3.—*γ-Globulin Therapy with Reference to Administration and Clinical Results*

Patients, No.	Diagnostic Groups	Injections, No.	Injected, Ml.	Clinical Results		
				Excellent	Good	Negative
25	I	Total 142	Total 3,060	9	9	7
		Avg. 6	Avg. 123			
5	II	Total 26	Total 580	2	2	1
		Avg. 5	Avg. 116			
1	III	Total 6	Total 120	1	0	0
		Avg. 6	Avg. 120			
11	IV	Total 58	Total 820	6	5	0
		Avg. 5	Avg. 75			
12	V	Total 62	Total 1,150	6	5	1
		Avg. 5	Avg. 96			
5	VI	Total 31	Total 620	1	3	1
		Avg. 6	Avg. 124			
—				—	—	—
59				25	24	10

Adults thus received on the average 3 gm. of γ-globulin fraction, which dose was reported by Bruton[1] to produce a surprising rise in γ-globulin titer with, however, a gradual return of γ-globulin to its previously low level. The half-life of parenterally administered γ-globulin is considered to be between 25 and 30 days.[4] Seltzer et al.[9] report the half-life value of γ-globulin in the newborn infant to be 30-35 days; in the child from 6 months to 8 years old, 20.3±2.8 days, and in adults, 13.1±2.8 days. There is some evidence that smaller doses at more frequent intervals, 5 ml. each week, produce better clinical response.

In our series, 59 patients received γ-globulin therapy for an average period of six months, with no patient being reported who did not receive treatment for at least four months (Table 3). We were limited in our study to 59 patients because, for economic and availability reasons, the American National Red Cross could not supply poliomyelitis immune globulin (human) unless the patient showed a γ-globulin level of minus 25% or lower. A total of 325 injections of γ-globulin were made representing the administration of 6,350 ml. of immune serum globulin (human).

The clinical response of our patients to γ-globulin therapy was excellent for 42%, good for 41%, and negative for 17%. Combining the excellent and the good results indicates that 83% experienced satisfying improvement. Controls consisted of the patients themselves. Since their dermatoses were extremely chronic, all had previously received the gamut of therapy and had reached a therapeutic plateau.

Those entities representing more active bacterial infection, as folliculitis and furunculosis and pyoderma, showed better clinical response, particularly in children. There were no failures for pyoderma and only one for furunculosis. The more indolent conditions, such as staphylococcic eczematoid dermatitis and seborrheic dermatitis, responded more slowly, required the greater number of injections, and showed the larger number of failures. The failures for those patients classified as staphylococcic eczematoid dermatitis could represent secondary staphylococcic infection on allergic dermatitis and psychogenic dermatitis.

The results for the pustular type of acne vulgaris were interesting. The γ-globulin determinations on these 20 patients showed 85% titers were below normal. We had an opportunity to report on only five patients treated, as the others had not received four or more injections. The results were one excellent, three good, and one negative. Schaffer et al.[10] reported similar experiences.

Reactions accompanying γ-globulin therapy are infrequent. In our series of 59 patients representing 325 injections, only

one definite reaction was observed. This consisted of erythema, swelling, tenderness at the site of injection, generalized urticaria, and fever (temperature 103 F) occurring three days after the injection. These symptoms regressed promptly following corticosteroid therapy. Owings [11] reports a severe anaphylactoid shock type of reaction following the first injection of γ-globulin. Murray and Ratner [12] report little danger of homologous serum hepatitis following the administration of immune serum globulin (human), particularly if it is produced by the cold-ethanol method.

Conclusions

It is indicated from the data presented here that the large majority of patients showing persistent staphylococcic dermatoses also have a marked hypogammaglobulinemia. In addition, there is a general lowering of serum antibacterial titers. Over 75% of all patients studied showed such a change. The loss of antibacterial activity was related, in part, to a deficiency in those substances found in blood which are inactivated at temperatures that destroy complement. Inasmuch as properdin is the only known natural component of blood which requires complement for bacterolytic activity, it is assumed that this protein plays an important role in the protective mechanism of those patients. It appears significant that of the 23 people in Table 2 who had less than 0.5 units of complement-depending activity all had electrophoretic patterns which showed remarkable lowered α- and β-globulin. Pillemer et al.[13] reported that properdin could be fractionated from serum in Deutsch's Fraction III. Approximately 70% of this fraction [14] is comprised of α- and β-globulins. Therefore, it seems likely that properdin is deficient in these patients.

In addition to the complement-depending factors, there are components normally present in serum which retain potent antibacterial activity after serum has been heated at 56 C for 30 minutes. It was found that the heat-stable antibacterial factors were also remarkably reduced from normal values. The identity and importance of these components are presently being investigated.

Many workers have reported that patients with repeated infections often show lowered γ-globulin levels. One might expect that patients with persistent chronic infections might also be deficient in this protein. Such, in fact, is the case as has been shown here. Besides a lowered immune potential, antibacterial substances found in serum which are related to natural resistance are reduced. Though most of the patients reported here fall into this general pattern, a diagnostic generalization should be avoided. Some of the clinically severe patients were found to have normal antibacterial and γ-globulin levels. Different combinations of these two factors were also observed, i. e., lowered γ-globulin with a normal antibacterial titer or the reverse of this. These exceptions only point to the extreme complexity of the problem of natural resistance.

Immune serum globulin (human) therapy benefited the majority of our patients who presented chronic staphylococcic dermatoses and low γ-globulin levels. We did not have the opportunity to observe the effects of γ-globulin therapy on those patients with chronic staphylococci dermatoses who had normal and elevated γ-globulin determinations.

Summary

In this study, patients who presented chronic staphylococcic dermatoses were studied: (1) 59% had a reduced γ-globulin level, (2) 70% showed a lowered total serum antibacterial activity, (3) 42% were deficient in the complement-depending (properdin) activity, and (4) 83% demonstrated satisfactory improvement following γ-globulin therapy.

141 E. 2d South St. (11).

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Lichen Striatus

A Study of Fifteen New Cases with Special Emphasis on the Histopathological Changes and a Review of the Literature

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The incidence of lichen striatus is so rare that when such a condition occurs we are more prone to discard it for one of the other commoner linear dermatoses, such as lichen planus, nevus unius lateris, linear psoriasis, and even herpes zoster. It is easily understandable that such confusion may occur when one realizes that, in spite of the statements by different authors,[1,2] a clear-cut clinical picture does not exist; that the therapeutic response is, as we shall see later, of no help at all, and that the histopathologic changes occurring in lichen striatus are still a confusing and undecided factor.

The diagnosis of lichen planus and psoriasis does not present any difficulty in cases where a widespread eruption is present, but we may also be confronted with a combination of lichen striatus and lichen planus, as the case described by H. Pinkus [3] has clearly shown.

The history of lichen striatus dates back to the end of the 19th century and the disease has been described repeatedly under different terms, such as lichenoid trophoneurosis,[4] neurodermite zoniform,[5] linear neurodermitis,[6] linear dermatosis,[7] strichfoermige eruption,[8] zonal dermatosis,[9] lichenoid eruption,[10] and lichen striatus.[11] We will, for practical reasons, limit the history of lichen striatus to a few names: Balzer, Mercier, Brocq, Besnier, Hallopeau, and Felix Pinkus. In 1889, at the session of the French Society of Dermatology and Syphilology, Balzer and Mercier [4] presented a case of lichenoid trophoneurosis in a linear pattern along the course of the lesser sciatic nerve. In the discussion that followed, Besnier, Hallopeau, and Brocq discussed the clinical differential diagnosis from other linear dermatoses, and it was Brocq who, on this occasion, first advanced the etiologic hypothesis later known as "locus minoris resistentiae," which is now almost unanimously accepted. He commented, "I think that there are persons who are affected by some congenital manifestations of the skin such that some zoniform regions are either temporarily or permanently more vulnerable and, for this reason, more susceptible to a dermatosis to which the subject might be exposed or predisposed."

The etiopathogenesis of lichen striatus has led students of the subject to innumerable theories, including a relation between the linear arrangement and the course of the blood vessels,[12] the lymphatics,[13] and the peripheral nerves.[14,15] Philippson,[16] in describing two cases of ichthyosis hystrix, saw in it a relation with the Voigt's lines,[17] which are the boundaries of the areas of distribution of the cutaneous nerves. Within these boundaries there was, presumably, an area of lowered resistance. Jadassohn,[18] Nicolas and Rousset,[19] and Touraine and Solente [20] attributed the linear distribution to the influence of the lines of implantation of the hairs. Metameric,[7] neuritic,[21] and embryologic [22] theories have also been suggested. According to Senear and Caro [1] and Rose [23] there is not, at present, an adequate theory to explain the primary cause of the linear eruption.

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TABLE 1.—*Summary of Clinical Findings by Different Authors*

Author	Age	Sex	Duration	Onset	Location	Symptoms	Character of Lesion	Other Condition
Senear & Caro [1]								
Case								
1	39	F	Few wk.	Gradual	From scapula to volar aspect of arm & forearm	None	Reddish papules & patches of dermatitis in linear pattern	
2	10	F	6 wk.	Rapid	Volar aspect of arm from wrist to shoulder	Mild pruritus	Lichenoid papules, single & coalescing; primary papule not typical of lichen palnus	
3	6	F	Several mo.	Not mentioned	From sternum to axilla to arm & cubital fossa	None	Pinpointed & BB-shot sized papules; color varying from that of normal skin to slight red, single & grouped, some glistening & some covered by scales	
4	3	F	3 wk.	Rather rapid	From ulnar side of right wrist upward	None	Lichenified linear streak; lesions reddish at first	
5	35	F	1 mo.	Sudden	From right ear to right clavicle	Not mentioned	Lichenified band	Lichen simplex chronicus
6	6	F	6 mo.	Not mentioned	Along radical side of left arm from cubital fossa upward	None	Pinheaded papules, single & coalescing & slightly elevated	
7	15	M	3-4 wk.		Left arm, dorsal surface	None	Individual & coalescing lichenoid papules in linear pattern; a linear stria on nail	T. pedis
8	10	F	Unknown	Not mentioned	From right scapula to shoulder, downward along outer aspect flexar surface of arm; turned over dorsal aspect of forearm to wrist & to base of thumb	Not mentioned	Linear streak of lichenification	L. urticatus
9	10	F	4 mo.	Gradual	From sternoclavicular joint laterally to left shoulder, downward over the front of the arm to wrist	Severe pruritus	Lichenified streak & pinhead-sized lichenoid papules having tendency to coalesce; 2 bands, which in their ascending and descending course met at the cubital fossa	
10	57	F	4-5 mo.		A streak, one on anterior surface, right shoulder; other extending from right cubital fossa extending downward to wrist	None	Pinhead-sized lichenoid papules	
Shaffer [21]	45	F		Sudden	Posterior leg from gluteal region to thigh, calf to toe	Severe pruritus	Slightly verrucous & linear	Kahn +
Johnson [22]	1	M	Few mo.	Sudden	Left half of body from head to foot	Not mentioned	Flesh-colored & verrucous linear lesion with some areas having lichenoid appearance	
Rothman & Neiderman [18]	1	F	2 mo. when seen 1st	Gradual (2-3 wk.)	Posterior area of right leg	None	Confluent, glistening pinkish yellow round papules, some covered by fine scales; discontinued linear distribution	

TABLE 1.—*Summary of Clinical Findings by Different Authors*—Continued

Netherton [28]	44	F		Burning & itching preceding rash	Posterior thigh, calf & lateral aspect of right foot	Mild pruritus since onset	Linear, superficial light to yellowish & pink, smooth & scaly single & grouped papules, no angular or umbelicated; Wickham striae not present	
Schmidt [33]	5	F	Mo.		Left arm	None	Single & coalescing flat or slightly raised lichenoid papules & macules in linear distribution	
Lewis [34]	13	F	Several mo.		Left arm	Not mentioned	Lichenoid discrete confluent scaly papules grouped in linear formation	
Pinkus, F.[8] Case								
1	26	M	Several mo.		Left arm	Pruritus first 2 days only	Reddish-brown slightly raised pinhead-sized, translucent, not scaly papules, isolated & grouped in linear distribution	
2	53	M	Few mo.		Forearm	Pruritus	Vesicles & papules in linear pattern; papules similar to lichenoid papules but of light translucent bright color	
Duperrat, Basset, & Baptista [35] Case								
1	8	F	About 1 yr.		Not mentioned	None	Discontinuous papules disposed in a linear pattern covered by a scale	
2	4		Few mo.		Posterior aspect of leg from buttock to heel		Interrupted streak of scaly papules	
Pinkus, H.[3]	37	M		Gradual	From right buttock downward, thigh to calf		Tiny flat somewhat scaly papules of brownish red color	L. planus
Beck [36]	12	F	Still present after 1 mo.		From gluteal fold to ankle; few papules on buttock same side		Linear streak & lichenified papules	
Frain-Bell [37]	11	F	7 wk.	Not mentioned	Posterior aspect of left leg; few lesions on abdomen		Combination of flat-topped papules & eczematous reaction; linear on calf, more plaque-like on thigh	
Lodin & Gentele [38]	57	M	30 yr.	Gradual	Right leg from little toe to heel & upward to buttock & scrotum	Severe pruritus	Linear lesion composed of reddish violet, flat, coalescing papules	
Semon [9]	47		3 yr.	Rapid spread	Face; left side of forehead	None	Weeping patches recurring during summer months; linear pattern	
Lee [7]	8	F	3-4 mo.	Rapid	Leg; inner aspect from thigh to malleolus	None	¼ in. wide linear band	

TABLE 2.—*Pathological Changes Reported by Different Authors*

Author	Epidermis	Corium
Senear & Caro [1]		
1	Irregular acanthosis with some lateral fusion of the rete pegs; few wandering cells; slight intercellular & much intracellular edema; basal layer intact & granular layer thinner & continuous	Inflammatory changes chiefly seen in papillary & subpapillary layer, accompanied by edema; blood vessels dilated & sharply surrounded by cellular infiltrate
2	Irregular acanthosis; moderate intercellular & considerable intracellular edema, latter overlying papillary inflammatory changes; epidermis at this point invaded by wandering cells; basal layer disorganized in proximity of intracellular edema	Some papillae edematous & filled with diffuse infiltrate of lymphocytes, histiocytes, connective tissue cells, & plasma cells; densely packed mantles of infiltrate around vessels in subpapillary part of corium & extending down about hair follicles
Lewis [24]	Hyperkeratosis & acanthosis	Inflammatory reaction mainly in region of hair follicles & extending between rete cones
Schmidt [22]	Slight acanthosis; basal layer intact	Focal collection in upper & deeper portion of corium; no dilatation of follicles or sudoriferous glands
Netherton [19]	Loose hyperkeratosis with small islands of parakeratosis; moderate, irregular acanthosis with slight intercellular & pronounced intracellular edema; wandering cells present in most edematous areas; granular layer thin & interrupted; basal layer intact	Edema of papillary & subpapillary layer, no inflammatory changes noted below subpapillary layer; blood vessels are dilated & surrounded by a loose perivascular lymphocitic infiltrate
Pinkus, F. [3]		
1	Hyperkeratosis with spotty parakeratosis; intercellular edema with some unevenly distributed vesicles; corps ronds in horny layer	Infiltration of papillary body & upper dermis around superficial and deep vascular tree
2	Same changes	Same changes plus involvement of sweat glands by infiltrate
Rothman & Neiderman [18]	Hyperkeratosis with parakeratosis; granular layer absent in most part of section; rete pegs broadened & confluent; Malpighian layer shows intercellular & intracellular edema; basal layer intact but lower part of epidermis invaded by wandering cells	Extensive edema in papillary & subpapillary dermis; infiltrate of lymphocytes & connective tissue cells sharply demarcated in subpapillary layer, but similar circumscribed round infiltrate also seen at junction of dermis & subdermis, particularly around sweat glands; vessels dilated with perivascular infiltrate
Shaffer [21]	Acanthosis with intra- and extracellular edema; hyperkeratosis with parakeratosis	Papillae edematous with considerable infiltrate of round cells & some polymorphonuclear leukocytes; blood & lymph vessels dilated with decided perivascular infiltrate
Duperrat, Basset, & Baptista [25]	Parakeratotic scales mixed with dry serum; granular layer not present; papillomatosis with normal basal layer except where papilla is infiltrated	Not mentioned
Pinkus, H. [2]	Acanthotic but thinner over affected papillae; lower strata dissolved by infiltrate, many cells transformed in eosinophilic corpuscles; granular layer normal or absent; horny layer partly normal & partly with parakeratotic scales containing dyskeratotic corpuscles	Papillary & subpapillary layers contain lymphocytic infiltrate extending downward as heavy mantles around blood vessels, apparently involving veins more
Lodin & Gentele [20]	Picture of chronic eczema neurodermatitis	
Semon [9]	Normal epidermis except for slight spongiosis & some vesicular spaces	Granulation tissue consisting of lymphocytes, histiocytes, & newly formed capillaries; infiltration extending throughout corium
Lee [5]	Loose hyperkeratosis; granular layer thinner; irregular acanthosis; inter- and intracellular edema; basal cells broken in places, especially in relation to papillae which were more infiltrated	Perivascular lymphocytic & histiocytic infiltrate; infiltrate most marked in papillae & superficial part of dermis; capillaries congested & hair follicles surrounded by pleiomorphic infiltrate; elastic tissue absent or diminished in areas of heavy infiltrate

TABLE 3.—*Summary of Clinical Findings in Fifteen New Cases*

Case No.	Age	Sex	Duration	Onset & Development	Location	Symptoms	Character of Lesion
1	64	M	3 mo.	Sudden	From shoulder to hand along extensor aspect of arm	None	Slightly raised & flat angular papules single & coalescing to form plaques suggestive of Lichen simplex chronicus; linear
2	68	F	3 mo.	Rather rapid	Began on volar aspect of wrist & spread upward along outer aspect of arm to shoulder	Mild pruritus	Flat topped shiny papules single & grouped in interrupted streak
3	18	M	8 mo.	Sudden	From right buttock down to popliteal fossa & heel	None	Reddish, single & coalescing papules, somewhat shiny and covered by a grayish scale; linear pattern
4	7	F	3 wk.	Sudden	Outer aspect of left thigh from knee to buttock	Slight pruritus	Isolated & confluent brownish papules, angular & flat in depigmented linear pattern
5	6	F	10 mo.	Slow; 4 mo.	From navel to perineal area downward along inner aspect of right leg to big toe	None	Hypertrophic almost verrucous
6	26	F	2 mo.	Slow	From hand along ulnar side of left arm up to shoulder & from here to anterior chest	Very pruritic	Purplish papules, single & coalescing in an interrupted streak, suggesting lichen planus
7*	9	M	1 yr.	Rather rapid	From right scapula to right shoulder down arm to right thumb	Occasional mild pruritus	Depigmented linear eruption 0.5 cm. wide, composed of tiny little red-colored papules
8*	13	M	1 yr.	Slow	Dorsal surface of left forearm, from elbow to thumb	None	Linear eruption formed by single & coalescing reddish papules; width of lesion about 2 cm.
9	29	F	7 mo.	Rapid	Anterior aspect of right leg	Mild pruritus	Linear eruption formed by coalescing papules having an erythematous, scaly, shiny configuration somewhat resembling lichen simplex chronicus
10*	30	F	Unknown 6 wk. when seen		From breast to axilla downward along ventral aspect of left arm	Pruritus	Linear arrangement of red papules, shiny and flat-topped; eruption began on axilla
11	9	F	2 yr.	Gradual 3 months	From left wrist upward to shoulder & scapula & down to wrist	None	Depigmented linear lesion formed by slightly raised tiny angular papules
12‡	22	F	2 mo.	Sudden appearance, full development reached slowly	From apex of scapula up to shoulder & axilla; from axilla anteriorly to breast & down to forearm	Occasional mild pruritus	Tiny depigmented papules, single & grouped, violaceous shiny plaques, & grayish shiny patches; interrupted linear band with width varying from few millimeters to 3-4 cm.
13†	3	F	6 mo.	Gradual	Posterior aspect of leg from buttock to heel	None	Rough, scaly, skin-colored linear lesion
14†	3	M	3 mo.	Gradual	Extensor surface of left arm, from hand to elbow	None	Irregular streak of papules somewhat depigmented, tiny flat & raised
15‡	57	F	3 mo.	Rapid onset; slow development	Chest; distributed along the course of the 5th & 6th rib & on medial aspect of left arm	None	Pinpointed, depigmented, erythematous papular eruption, some flesh-colored; linear pattern

* Patient failed to return.
† Patient is still under observation.
‡ Patient has improved 90%.

TABLE 4.—*Summary of the Pathological Changes Seen in the Fifteen New Cases Described in Table 3*

Case No.	Epidermis	Corium
1	Irregular acanthosis with hyperkeratosis & spotty parakeratosis; occational dyskeratotic grain & cells in horny & granular layer; areas of intercellular & intracellular edema overlying dermal infiltrate; granular layer normal or thinner; some lymphocytes migrated from dermis with secondary disruption of basal layer	Heavy perivascular lymphocytic & histiocytic infiltrate in superficial & deep corium; some papillae heavily infiltrated with damage of overlying epidermis
2	Slight acanthosis with generalized hyperheratosis & parakeratosis in spots; parakeratosis related to areas of increased epidermal damage; granular layer normal or thinner; rete disrupted in several places by infiltrate from dermis; inter- & intracellular edema with some vesiculation; occasional grain-like dyskeratotic cells present	Superficial vascular net outlined by inflammatory infiltrate of lymphocytes & fixed cells; occasional spreading of infiltrate around hair follicles with following damage and atrophy; some slides present mainly dermal changes, other ones more epidermal changes
3	Normal thickness with few areas of irregular acanthosis; hyperkeratosis with occasional parakeratosis; granular layer normal; inter- & intracellular edema with tendency toward vesiculation; few lymphocytes present; basal layer normal except for occasional disruption; epidermal changes closely related to underlying dermal changes	Histiocytic & lymphocytic infiltrate surrounding blood vessels & descending from papillary layer to medium corium; elastic fibers not present in areas of heavy infiltrate
4	Hyperkeratosis & spotty parakeratosis; absence of granular layer in circumscribed areas correspondent to severe changes of rete; in same areas edema & inflammatory infiltrate with occasional presence of individually keratinized cells	Vascular net outlined by lymphocytic and histiocytic infiltrate present in superficial, medium, and deep corium, producing atrophy of sebaceous glands & disturbance of follicular epithelium
5	Regular epidermis with areas of acanthosis & atrophy, related to papillary & subpapillary perivascular infiltrate; hyperkeratosis with occasional parakeratosis; some intercellular edema sporadically	Perivascular lymphocytic infiltrate distributed through subpapillary & middle corium; occasionally hair follicle involved with changes leading toward its destruction.
6	Normal epidermis with slight general thickening & few areas invaded by lymphocytes from below; hyperkeratosis with spotty parakeratinized cells	Perivascular mainly lymphocytic infiltrate in superficial, medium & deep corium, elastic fibers missing in areas of infiltrate
7	Normal epidermis except for areas secondarily affected where there is intercellular edema connected to areas of dermal infiltrate; hyperkeratosis; normal granular layer	Lymphocytic & histiocytic infiltrate, partly subepidermal, partly perivascular extending down to level of sweat gland, & partially perifollicular with secondary atrophy; some pigment carried down out of epidermis & taken up by histiocytes
8	Normal except for few areas of intercellular & intracellular edema related to underlying damage; hyperkeratosis with occasional parakeratosis; normal granular layer	Normal corium except for band-like infiltrate of lymphocytes & fixed cells surrounding vessels, mostly in subpapillary layer; occasionally papilla involved with production of secondary epidermal changes
9	Hyperkeratosis with occasional parakeratosis related to area of damage; intra- & intercellular edema & some lymphocytic infiltrate	Perivascular infiltrate of lymphocytes & histiocytes in subpapillary and middle dermis; occasional papilla involved
10 (2 biopsies)		
(*a*)	Normal epidermis	Perivascular lymphocytic & histiocytic infiltrate
(*b*)	Basal & prickle layer almost gone due to edema & lymphocytic infiltrate with formation of vesicles; hyperkeratosis & occasional parakeratosis; few dyskeratotic cells	Perivascular lymphocytic & histiocytic infiltrate
11	Normal thickness & occasional damaged areas; hyperkeratosis with occasional parakeratosis; granular layer normal, inter- & intracellular edema & mononuclear-cell infiltrate	Perivascular lymphocytic infiltrate extending down to sweat glands; some hair follicles involved; in some areas infiltrate mainly papillary
12 (2 biopsies)		
(*a*)	Normal thickness; some intercellular and intracellular edema; occasional dyskeratotic cells; normal granular layer; few lymphocytes; basal layer generally intact	Perivascular mononuclear cells infiltrate mainly in superficial dermis
(*b*)	Occasional areas of acanthosis with hyperkeratosis; in these areas granular layer thicker than usual; lymphocytic infiltrate with moderate destruction of basal layer	Perivascular infiltrate especially heavy in papillary & subpapillary layer; areas of perivascular infiltrate scattered also in deep corium
13	Normal with occasional involved areas; hyperkeratosis with spotty parakeratosis; normal granular layer; dyskeratotic cells all through section; some lymphocytes infiltrated from dermis	Pronounced lymphocytic & fixed tissue cells; perivascular infiltrate in all strata of corium
14	Normal thickness except for areas of thinning due to infiltration from below; in these areas basal cells practically destroyed & loss of pigment carried down in dermis	Lymphocytic infiltrate in widened papillae & extending downward along blood vessels to deep corium
15	Epidermis invaded by mononuclear inflammatory infiltrate from below, with epidermal structure rather disrupted; occasional dyskeratotic cells; hyperkeratosis; normal granular layer	Heavy subepidermal, perivascular lymphocytic & histiocytic infiltrate extending to deep corium

In a recent study, Asang,[24] working with a fetal monster, divided the lines of the lower extremity into three types: Trennlinie, Grenzlinie, Sammellinie. According to his drawings, these lines represent the boundaries not only between one nerve and another but also between branches of the same nerve. These areas seem, in the lower extremity, to fit the distribution of lichen striatus in some of the cases. However, in agreement with Senear and Caro[1] and Gougerot and Lortat-Jacob,[25] whatever the primary factor may be, there are, apparently, in the body fragile zones of congenital origin. Kreibich's experiment,[26,27] by which he produced a dermatitis confined to definite lines after central and peripheral nervous stimulation in neuropathic persons, supports the view that in the skin there are linear zones of increased reactivity.

The first histopathologic description of lichen striatus is that of Felix Pinkus.[8] According to him the main changes occur in the dermis, with a secondary involvement of the epidermis. The same changes have been described repeatedly by other authors,[2,23, 27,28] and they were, apparently, typical enough to confirm the theory that lichen striatus was a new entity. However, Senear and Caro[1] and others[30] were more inclined to consider them as those seen in chronic dermatitis or neurodermatitis.

In order to clarify some of the clinical and pathologic findings, a review of the past literature and an analysis of 15 new cases was made.

Tables 1 and 2 represent a summary of the past literature, while Tables 3 and 4 are a summary of the findings of the 15 new cases. Three of these cases will be discussed in detail because they represent three somewhat different clinical pictures of the same disease.

Report of Cases

CASE 1.—A 64-year-old white man, one month before being seen, developed a sudden linear dermatosis, completely asymptomatic, on the right arm, descending from the shoulder to the hand along the lateral aspect of the arm. The lesion consisted of papules slightly raised and flat, angular in appearance, forming plaques that had the typical picture of lichen simplex chronicus with a glistening surface. The line was somewhat continuous and 0.5 to 1.5 cm. wide. During a two-month period, the patient received four x-ray treatments, for a total of 200 r. After this two-month period the dermatosis was still present, although somewhat less distinct, and characterized by a few scattered reddish papules.

Histologic examination showed in the epidermis occasional areas of acanthosis with hyperkeratosis and spotty parakeratosis. Dyskeratotic grains and occasional cells were visible in the parakeratotic layer and the granular layer. Areas of intracellular and intercellular edema were present where the epidermis was overlying the dermal infiltrate. Some lymphocytes migrated from the dermis into the epidermis and, in these areas, the basal layer appeared to be disrupted. The corium presented a heavy lymphocytic and histiocytic infiltrate, which was mainly perivascular and also descended with the vessels into the deep corium. Some papillae were heavily infiltrated, with an evident damage of the overlying epidermis.

CASE 5.—A linear lesion began to develop in a 6-year-old white girl in December and extended slowly from the navel to the perineal region and from there along the inner surface of the right leg to the big toe. The eruption reached its full development 4 months later, and it disappeared spontaneously 10 months from the onset. The patient was asymptomatic all through the course of the disease. The dermatitis was rather hypertrophic and verrucous in character. The biopsy specimen showed a rather regular epidermis, except for some areas of acanthosis and atrophy; both of these changes were related to a papillary and subpapillary perivascular infiltrate. There was diffuse hyperkeratosis with occasional mild parakeratosis, related to the underlying infiltrated papillae. Some intercellular edema was occasionally found. The dermis showed a perivascular lymphocytic infiltrate, which rarely involved a papilla and was mainly distributed through the subpapillary corium and middle corium. Occasionally, the same infiltrate surrounded the hair follicle, with changes of the follicle varying from infiltrate and edema of epithelial cells to a complete destruction of the hair follicle.

CASE 12 (Fig. 1).—A 22-year-old Negro woman, two months before she visited our department, noticed a sudden rash on the left shoulder, from which three distinctive streaks originated, one heading toward the apex of the scapula; a second, downward along the extensor surface of the arm to the forearm, and, finally, a third one which, by passing along the anterior axillary fold, was reaching the breast. The complete development

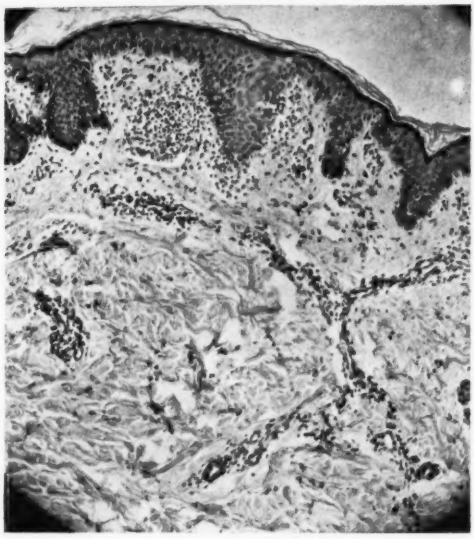

Fig. 1.—Perivascular infiltrate in papillary, subpapillary, and mid dermis. Slight changes in the epidermis. Hematoxylin and eosin; ×90.

was reached in a period of two weeks, and an occasional mild pruritus occurred.

The streak was formed by single papules and plaques. The papules were tiny and rather depigmented compared to the surrounding skin; they were somewhat suggestive of those that we find in lichen nitidus. The plaques were of different shades. Some formed, apparently, by coalescence of the previously described papules; others were somewhat suggestive of neurodermatitis, and still others were rather reddish violaceous, with a glistening surface, and more suggestive of lichen planus. The linear distribution was not continuous, and it varied in width from a few millimeters to several centimeters. The lesion was still present after three months, during which time no treatment was administered. During the fourth month, the lesion gradually began to fade, and in a period of two weeks the skin became completely clear.

Two biopsies were performed, one from an older plaque suggestive of lichen planus and the second from a younger lesion. The first biopsy specimen presented an epidermis which was normal, atrophic, and acanthotic in spots. The dermal infiltrate affected some papillae more than others. The area of acanthosis also showed an increased thickness of the granular layer, with some lymphocytic infiltrate and destruction of the basal layer. The perivascular infiltrate extended downward to the deep corium.

The second biopsy specimen showed a perivascular mononuclear infiltrate, mainly localized in the superficial dermis. The epidermis was of normal thickness and showed some intercellular and intracellular edema. Few lymphocytes were present, and occasional dyskeratotic cells and grains were found in the granular and horny layer. The granular layer was normal throughout the section.

Comment

A comparison between my new (Table 3) cases and those collected in the literature (Table 1) has limited value, for in many of the cases so far described the diagnosis was based on purely clinical findings without a pathologic evaluation.

From the examination, history, clinical description, and pathologic findings of 15 cases, 10 were found to be female and 5 to be male; 8 were over 15 years of age, while 7 were under 15 years of age. The sex distribution corresponds to the findings of other authors (Table 1), where out of 26 patients 18 were female and 6 were male (in 2 cases sex was not mentioned). However, the findings regarding the age show a marked discrepancy; the rate among adults and children in my count is almost equal, whereas in the review of other cases we found a rather striking increase of lichen striatus during childhood.

Lichen striatus involves mostly the upper and lower extremities, with a preference for the former (2:1). It is always unilateral,

and, when affecting a limb, it may also spread to the chest or abdomen. At the same time, lichen striatus may have its origin on the chest or abdomen and from there may spread to other parts of the body. It is generally asymptomatic, but it may occasionally be associated with every degree of pruritus.

The onset is generally sudden, and it reaches its full development in a period of time that may vary from a few days to several weeks. The eruption frequently begins as a plaque or group of irregularly scattered papules, eventually reaching a linear pattern. However, it may remain without a linear pattern for several weeks. It is possible that, if the trigger mechanism discontinues its action, we may find an atypical eruption of lichen striatus sine striatione.

The clinical picture does not appear to us to be as clearly distinct as when described by other authors.[1,2] If the diagnosis could be made solely on the history and the clinical evaluation and with the aid of other important findings one could discriminate better between lichen striatus and other linear dermatoses; however, this alone is certainly not sufficient. If we consider only Cases 1, 5, and 12, described in detail, we have three distinct clinical pictures. In Case 1, had the lesion not been linear in shape and asymptomatic it could easily have been mistaken for lichen simplex chronicus. Only two months later, during the involuting phase, the lesion consisted of scattered single reddish papules. Case 5 was verrucous in character, and it was clinically diagnosed as nevus unius lateris. Case 12, by contrast, was a collection of single hypopigmented papules, almost suggestive of lichen nitidus; patches formed by coalescence of such papules; violaceous plaques more suggestive of lichen planus, and, finally, grayish patches suggesting lichen simplex chronicus. On the basis of common histologic findings, it was felt that all these lesions were different stages of evolution of the same condition. Thus, clinical observation is not, in itself, sufficient to arrive at a diagnosis of lichen striatus.

Lichen striatus is unilateral and presents itself as an irregular streak of variable length and width, either continuous or interrupted, often dividing and again coalescing. The primary lesion is a papule that may be of different size, shape, and color. It may be isolated but more often coalesces to form plaques. The papules are generally slightly raised, flat, and angular; at times reddish and purple, and at other times somewhat shiny and covered by grayish scale. Generally, in the skin of a Negro the eruption appears hypopigmented in comparison to surrounding skin. Occasionally, small and tiny papules can be found, and infrequently an occasional vesicle is present. On one occasion, as in a similar case described by Johnson,[32] the eruption appeared to be formed by hyperkeratotic coalescing papules, suggesting, in its linear pattern, the nevus unius lateris.

The pathologic changes in lichen striatus seem to consist primarily in perivascular lymphocytic and histiocytic infiltrate (Figs. 1, 2, and 3), which may be present at any level in the corium and which when located around the hair follicles and sebaceous glands may produce secondary changes leading to atrophy of these organs (Figs. 4 and 5). The infiltrate presents always the characteristic perivascular pattern already described by F. Pinkus.[8] The epidermal changes are secondary to the perivascular dermal infiltrate, and they are found mostly when the infiltrate is present in the papilla or in the superficial subpapillary layer. Sections may be found where, besides the perivascular dermal changes, there is not any evidence of epidermal damage, while in other sections the epidermis may be found to be damaged in irregular areas alternating with normal epidermis, slight acanthosis, and atrophy.

The epidermal changes consist of variable stages of intercellular and intracellular edema, rarely resulting in early vesiculation. The basal cells are disrupted when closely related to the infiltrate and a scattered and

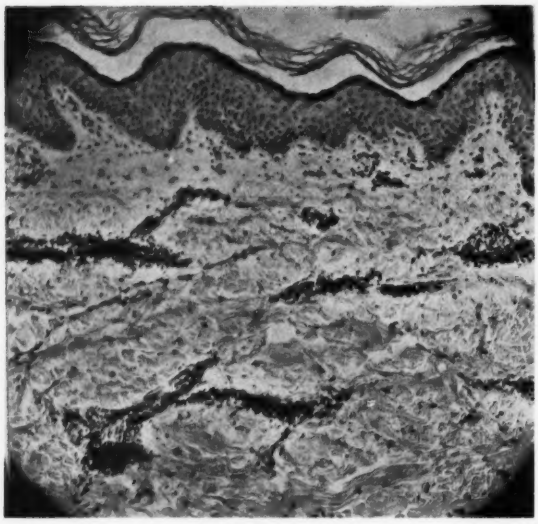

Fig. 2.—Normal epidermis and perivascular infiltrate in the subpapillary layer and middermis. Hematoxylin and eosin; × 90.

variable lymphocytic infiltrate has penetrated from below. Diffuse hyperkeratosis is present, and in a great number of sections there is also a spotty parakeratosis. The granular layer is generally normal or thinner, but on rare violaceous plaques, clinically suggesting lichen planus, it has been found to be thicker. It is worth noting that in this same lichen planus-like lesion nothing else except the hypergranulosis and acanthosis suggested the diagnosis of lichen planus histologically.

An important fact which was emphasized in the early description of lichen striatus by Felix Pinkus [8] and later on by Hermann Pinkus [3] is the presence of Darier cells and grains in lichen striatus. In a careful examination of the slides of these 15 new cases I found such dyskeratotic cells to be present almost in half (7) of the cases. They are found, however, in a small number, scattered mostly in the granular and horny layer (Fig. 8). Occasionally, some may be found in the prickle-cell layer. They never assume the proportions we see in Darier's keratosis follicularis. In Negro patients hypopigmentation was found to be due to loss of melanin from disruption of the basal layer. The pigment was picked up by melanophores and carried down into the corium.

In the differential diagnosis lichen planus, linear psoriasis, and nevus unius lateris have been mentioned. Linear neurodermatitis also should be considered.

Cases, like the one presented at the last International Congress in Stockholm,[30]

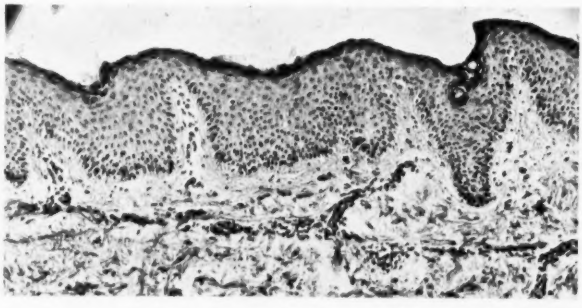

Fig. 3.—Subpapillary perivascular infiltrate. Slight epidermal acanthosis. Hematoxylin and eosin; × 90.

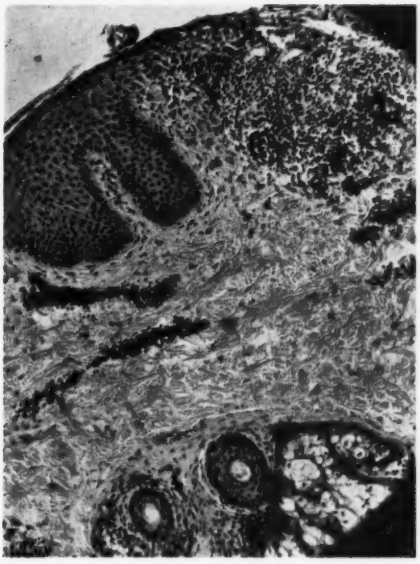

Fig. 4.—Destruction of the epidermis to the right; acanthosis to the left. The infiltrate is also present around the sebaceous glands with initial destruction (*x*). Hematoxylin and eosin; × 90.

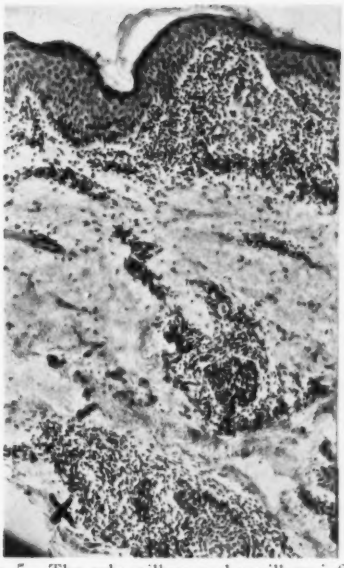

Fig. 5.—The subpapillary and papillary infiltrate is producing atrophy of the epidermis. The perivascular infiltrate has infiltrated and disrupted the hair follicle with gradual disappearance of the sebaceous gland (*x*). Hematoxylin and eosin; × 90.

which was intensely pruritic, had been present for 30 years, and was histologically described as chronic neurodermatitis, probably are a linear form of lichen simplex chronicus, and although some clinical similarity exists with lichen striatus, they should not be confused with it. Recently, the case of a child with typical infantile eczema was observed who had developed a linear eruption on the flexor surface of the forearm that histologically was typical of neurodermatitis and had none of the characteristics of lichen striatus.

The points of differentiation from lichen planus are many, but where some similarities may exist (hypergranulosis, acanthosis)

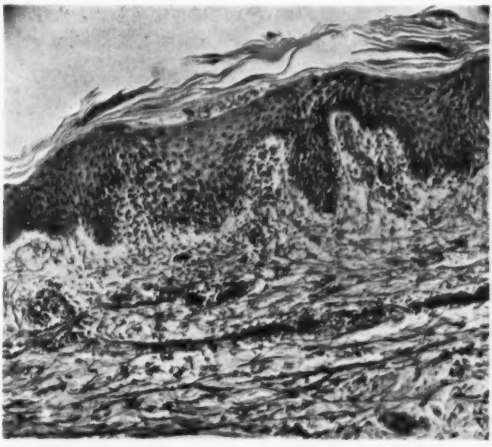

Fig. 6.—Acanthosis and spongiosis; infiltrate disrupting the basal layer. Subpapillary perivascular infiltrate. Orcein and Giemsa stain; × 90.

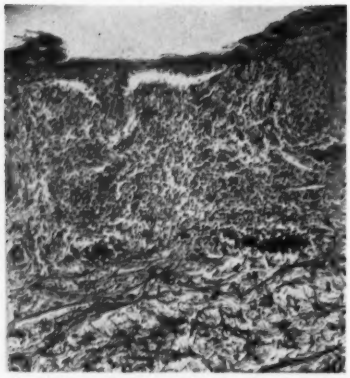

Fig. 7.—Heavy infiltrate in the papillary dermis with complete absence of elastic fibers, atrophy of the epidermis and parakeratotic scale. (From same case as Fig. 6.) Orcein and Giemsa stain; × 90.

a good differential point is that in lichen striatus the perivascular infiltrate affects (in contrast to lichen planus) some papillae and the overlying epidermis more than others in the same papule.

Psoriasis, although occasionally confusing clinically, presents a clear-cut typical histologic picture under the microscope.

Nevus unius lateris appears in childhood and exceptionally in early adult life. Occasionally, (Meirowsky)[37] it may disappear spontaneously. Histologically it presents a completely different picture from lichen striatus. There is hyperkeratosis of the epidermis, or of the opening of the hair follicles, with a variable degree of acantho-

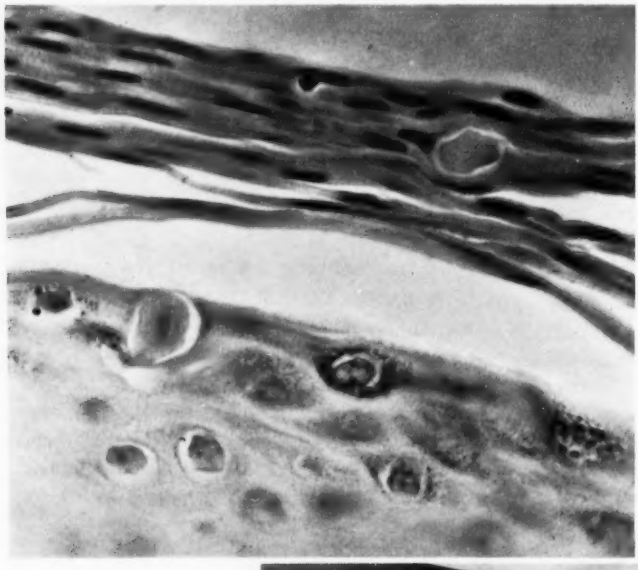

Fig. 8.—Details of parakeratosis and dyskeratotic cells. Hematoxylin and eosin; × 1,100.

Fig. 9.—Clinical picture of Case 12, Table 3.

sis and papillomatosis. At times, it may also resemble verruca plana, with a basket-weave appearance of the keratin layer and vacuolation of the cells of the granular layer.

The histologic picture of lichen striatus, although typical of this condition in differential diagnosis from other linear dermatoses, has a relative value when compared to the broad field of other dermatoses. Certain cases of parapsoriasis in plaques and possibly certain cases of toxic dermatitis with prominent involvement of the blood vessels can give a similar histologic picture, but it is obvious that the clinical picture would be completely different.

Lichen striatus is a self-involuting condition. In all my cases, it was not specifically affected by any form of treatment, including x-ray, and if improvement occurred, I felt that it was purely coincidental.

Conclusion

Lichen striatus is a polymorphic papular linear eruption, characterized by a rather rapid onset, lack of symptoms, and unilateral distribution. It has a rather prolonged course, varying from a few weeks to one year, and is not responsive to treatment. The papules may be flattened, glistening, and angular and either brown, red, or violaceous. They may be single or may coalesce to form plaques of different sizes. Recovery takes place without leaving any abnormality of the skin. The main pathologic changes consist of an infiltrate mainly centered around the subpapillary vessels and usually extending farther down, so that the vascular tree appears outlined by the infiltrate. The infiltrate is mostly composed of lymphocytes and histiocytes. Plasma cells are absent or rare. The epidermal changes appear to be secondary. In contrast to eczematous dermatitis, there is usually no acanthosis; there even may be atrophy, even though the epidermis is invaded by wandering cells which disrupt the basal layer and cause intercellular edema and even small vesicular spaces. Some parakeratosis is usually present. One feature which is often present in greater or less degree is individually keratinized cells, which never assume the proportions seen in Darier's disease.

Dr. Hermann Pinkus, Chairman of the Department of Dermatology, Wayne State University, and the following doctors collected and followed these cases: Dr. T. D. Arlook, Elkhart, Ind.; Dr. Lee Carrick, Detroit; Dr. Chester Farmer, Laurel, Miss.; Dr. Merle A. Haanes, Pontiac, Mich.; Dr. Frank Horne, Rocky Mount, N. C.; Dr. R. Laubenheimer, Milwaukee; Dr. Irving D. London, Montgomery, Ala.; Dr. T. H. Miller, Detroit; Dr. Betty B. Owens, Middletown, Ohio; Dr. A. E. Palmer, Detroit, and Dr. C. E. Reyner, Detroit.

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Prophylactic Management of Recurrent Seasonal Bacterid

Report of a Case

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According to the concept of bacterids, foci of infection in the tonsils, teeth, sinuses, or some other portion of the body discharge toxins or bacterial products into the circulation, producing culturally sterile pustules or vesicopustules on the hands and feet. The lesions usually appear first on the midportions of the palms and soles, from which they spread to cover all of the volar surfaces and often the lateral aspects of the hands and feet. Advanced cases are bilaterally symmetrical and entirely pustular, with distinctive histologic findings. Exacerbations and remissions are frequent, but local therapy affords no relief. Eradication of the foci of infection, however, will effect a prompt cure. The patients are generally middle-aged adults, and the disease is commoner in women than in men.

All dermatologists do not accept this theory. It seems desirable, therefore, to record well-studied cases whose manifestations support this concept and at the same time exhibit features that differ from the usual findings.

Report of Case

An 18-year-old male Negro high school athlete came to the Skin Clinic of the Reading Hospital on Nov. 29, 1957, complaining of a rash on his hands that interfered with his playing basketball. He stated that a similar eruption had occurred on his hands and feet every winter for the past seven years, the rash appearing in September and fading away in June. At times during the winter the eruption would improve considerably. Various local remedies had failed to influence its course.

Submitted for publication July 30, 1958.

From the Department of Dermatology, the Reading Hospital.

Fig. 1.—Firm shotty papules on backs of the hands and fingers. Note spindling of the digits.

His family and social history yielded no clue as to the cause of his complaint. In his personal history, a valuable lead was discovered in that every winter since early childhood he had had frequent sore throats and attacks of nasopharyngitis.

Upon examination, about 50 firm shotty hyperpigmented or depigmented papules were noted on the backs of his hands, wrists, and fingers (Fig. 1). Half that number of similar lesions were present on the dorsal surfaces of the feet. The palms and the volar and lateral aspects of the fingers exhibited 20 deep-seated vesicles and pustules (Fig. 2), but only a solitary pustule was found on the

Fig. 2.—Deep-seated pustules and vesicopustules on the palms and fingers.

left great toe. A laceration, due to a recent injury, was present on the back of the left hand. Some of the lesions were tender, especially when he would grasp an object, such as a basketball.

His fingers, particularly the third and fourth, were spindle-shaped, owing to swelling of the proximal interphalangeal joints. This feature caused him no trouble, and he had never been aware that the digits differed from the normal in shape.

The urinalysis showed 1+ albumin and 50-60 white blood cells. Routine serologic studies for syphilis and a complete blood cell count were normal. The seasonal occurrence of the eruption suggested a search for cryoglobulins, but none was found. The total proteins were 8.4 gm.; albumin, 4.8 gm., and globulin, 3.6 gm. per 100 cc. of serum, with an A/G ratio of 1.3:1. Staphylococcus pyogenes var. albus, coagulase-negative, was found in some cultures of the pustules on the fingers, but repeated examinations for fungi were unproductive.

A search for foci of infection was instituted. Dental x-rays revealed abscesses at the apices of three teeth, and cultural studies of the throat showed β-hemolytic streptococci. Following this lead, appropriate tests revealed an antistreptolysin titer of 2,500 Todd units and a Westergren sedimentation rate of 26 mm. (normal 0-15 mm.). The test for C-reactive protein was negative.

Because of the arthritic changes in the fingers, which x-rays established as due to soft tissue swellings, we were concerned with possible cardiac involvement. A cardiologist upon examination of the heart, however, reported normal findings, which were confirmed by negative x-ray studies of the chest and an electrocardiograph.

A discrete recent pustule was removed from the anteromesial aspect of the left fifth finger for histologic examination. The pathologic picture was found to be in essential agreement with that reported by Andrews[1] and others as occurring in pustular bacterid. The striking feature was a unilocular intraepidermal pustule. There was slight acanthosis, but the roof of the lesion revealed a normal granular and horny layer. A moderate infiltrate of lymphocytes, histiocytes, and scattered neutrophils was situated in the underlying corium, but only a few polymorphonuclear cells were present in the epidermis surrounding the pustule. The latter contained a net of fibrin, a few polymorphonuclear cells, and epithelial debris.

The tentative diagnoses of recurrent seasonal bacterid and rheumatoid arthritis having been made, treatment was initiated on an outpatient basis. The dental department began to extract the infected teeth. Cultures from the several tooth sockets showed an α-hemolytic Streptococcus. During this time, he received 600,000 units of benzathine penicillin G intragluteally twice a week, the β-hemolytic Streptococcus recovered from the throat having been found to be sensitive to that antibiotic. In spite of this therapy, he experienced a mild exacerbation of his eruption after each extraction. Since the over-all process was gradually becoming worse, he was admitted to the hospital on Jan. 3, 1958.

Upon admission, nothing remarkable was found in his general physical examination except enlarged tonsils with slight regional adenopathy. An otolaryngologist succeeded in expressing pus containing β-hemolytic streptococci from the left tonsil and recommended tonsillectomy. The patient was given 400,000 units of repository penicillin procaine intragluteally every 12 hours. Within a few days, β-hemolytic streptococci could no longer be recovered from his throat; the antistreptolysin titer had fallen to 1,250 Todd units, and the lesions on his hands showed marked improvement.

The patient's tonsils were removed on Jan. 11, 1958, under local anesthesia. Repository penicillin procaine, 400,000 units twice a day intragluteally, was continued postoperatively. The bacterid showed progressive improvement, and upon his discharge, on Jan. 18, 1958 pigmented and apigmented macules only remained on his hands, together with a few dark brown remnants of the previous lesions on the feet. The swellings of the interphalangeal joints had likewise all but disappeared.

The lad returned to the outpatient department one month later as a thoroughly dissatisfied patient. He had begun to develop new lesions on his hands and feet immediately upon his discharge from the hospital, and their numbers had increased until the clinical picture was about that of the previous November. The swelling of the fingers had recurred also, although this manifestation caused him no concern.

Earlier laboratory and clinical studies were repeated. The results were essentially those of our previous findings, including a β-hemolytic Streptococcus in his throat. In addition, a urologic examination and culture of the urine were noninformative.

Repository penicillin procaine, 600,000 units, was then administered intragluteally on 10 successive days. After this intensive course of therapy, β-hemolytic streptococci had disappeared from his throat and there was marked clinical improvement. At that time, prophylactic therapy was considered advisable. Accordingly, benzathine penicillin G, 1,200,000 units, was administered intragluteally every two weeks, and on the same occasion, a culture of his throat was taken. Under this regimen, his throat remained free of β-hemolytic streptococci and the skin approached normal. Only an occasional small short-lived vesicopustule would appear on his fingers from time to time, but the

feet remained clear. Upon his graduation from high school, at the end of May, he joined the armed forces.

Comment

This patient was unusually young for pustular bacterid, and involvement of the dorsal surfaces of the hands and feet was an atypical manifestation. His race, the histologic picture, the absence of psoriatic lesions elsewhere, and the response to penicillin were against the possibility of pustular psoriasis. There are few who would question the removal of his three abscessed teeth, but there are possibly some who may doubt the wisdom of his tonsillectomy, insofar as it failed to relieve his manifestations. It must be recalled, however, that prior to tonsillectomy benzathine penicillin G, 600,000 units administered intramuscularly twice a week, failed to eradicate β-hemolytic streptococci from his throat, whereas postoperatively benzathine penicillin G, 1,200,000 units given intragluteally every two weeks, was sufficient to eliminate that organism from cultures of his throat.

Prophylactic therapy to control streptococcal infections has been found effective in preventing recurrences of rheumatic fever. Wood et al.[2] compared the effectiveness of 1,200,000 units of benzathine penicillin G intramuscularly every four weeks, 1 gm. of sulfadiazine by mouth daily, and 200,000 units of oral penicillin daily in children who had had that disease. The streptococcal infection rate per patient year was least for the group receiving penicillin injections. For this reason, injections of benzathine penicillin G were chosen for our patient, although similarly favorable results may have been obtained by oral sulfadiazine. Prophylactic therapy with either of these agents may be the solution to those cases of pustular bacterid in whom removal of obvious foci has failed to eliminate the chronic infection.

As in the prevention of rheumatic fever, the question arises as to how long prophylactic therapy will be necessary in the future to prevent a recurrence of the pustular bacterid in this boy. We feel that frequent observations of his skin and cultures of his throat, beginning early next fall, will determine the answer to his problem.

Summary

A case of recurrent seasonal morphologically atypical pustular bacterid associated with rheumatoid arthritis is reported in an 18-year-old Negro high school athlete. The process appeared to have been caused by a chronic β-hemolytic streptococcic infection of the throat. Tonsillectomy failed to relieve his manifestations, although the disease was more responsive to penicillin postoperatively. Long-acting penicillin administered prophylactically every two weeks eliminated pathogenic streptococci from his throat and reduced his cutaneous manifestations to an occasional small short-lived vesicopustule.

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Seasonal Ragweed Dermatitis

Association of Immediate and Delayed Types of Pollen Sensitivity

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Introduction

Evidence for the etiologic role of ragweed pollen in the production of seasonal dermatitis has been well documented.[1-4] Although possessing the common denominator of hypersensitivity, there are two distinct morphologic types of ragweed dermatitis, each dependent upon a different immunologic mechanism. One is typical atopic dermatitis associated with an immediate intracutaneous whealing response to the water-soluble pollen fraction, mediated through circulating serum reaginic antibody to ragweed. Here, the challenging exposure to wind-dispersed pollen grains occurs through the inhalant route. The second variety is allergic eczematous dermatitis of the contact type, mediated through a tissue-sensitizing factor and demonstrated by the delayed epidermal response to patch testing with the ether-acetone-soluble pollen fraction, "ragweed oil." This is further characterized by an inability to detect circulating serum antibody in the patient whose exposure to the oil-containing ragweed pollen, leaf, or stem is by direct cutaneous contact.

Recent experience has demonstrated the coexistence of both atopic and contact factors in two ragweed-sensitive patients with seasonally aggravated dermatitis. A search of the literature pertaining to pollen sensitivity and dermatitis failed to reveal previously reported instances of these combined clinical entities. It was therefore felt noteworthy to report the clinical features of these two unusual patients as well as to record experimental findings that might contribute to an understanding of some aspects of the basic immunologic phenomena involved.

Submitted for publication July 17, 1958.

From the Department of Biology, Wilkes College; Associate Professor of Biological Research.

Report of Cases

CASE 1.—A 46-year-old white, male, agricultural worker, residing in Pennsylvania, was first seen in October, 1954, after an acute flare-up of recurrent seasonal rhinitis, dermatitis, and asthma. Since 1940, he had been subject to recurrent symptoms of lacrimation, ocular itching, sneezing, serous nasal discharge, coughing, wheezing, dyspnea, and a localized dermatitis of the eyelids, face, neck, and flexor surfaces of the elbows and knees. For the first two years these symptoms were present only during the months of August and September, but gradually nasal and chest symptoms began to appear earlier (May-June) and persist for longer periods of time (until January). Progression continued until his symptomatology at the time of this first examination consisted of mild recurrent perennial nasal and asthmatic symptoms, with an occasional flare-up of the dermatitis during the winter months, a slight increase of these symptoms during the early summer months, and severe exacerbations in August and September. Known aggravating factors included exposure to flowering vegetation, house dust, wool, and soap powders and eating oranges, grapefruit, pineapple, cucumbers, and melons. There were no other systemic symptoms or associated allergic manifestations.

Physical examination revealed a well-developed, well-nourished 46-year-old white man whose only positive physical findings were limited to the nose and skin. The nasal mucosa was pale and edematous; the turbinates, boggy, and the nasal secretion, serous. The neck, face, and flexor surfaces of the elbows and knees were involved with a dermatitis characterized by erythema, papule formation, and lichenification, and the skin generally exhibited white type dermatographism. The remainder of the findings were within normal limits.

Laboratory Studies.—The nasal smear was predominately eosinophilic. Blood cell counts were within normal limits, with 5% eosinophilia on differential smear. Urinalysis was negative.

Skin Tests.—On intracutaneous testing there were marked positive whealing responses noted to house dust, feathers, Alternaria mold, and ragweed pollen. Moderate responses were noted to silk, tobacco, wool, grass (timothy, orchard, blue) pollens, and a few food extracts, including coffee, corn, onions, oranges, peanuts, pork, and rye.

Clinical Course.—In addition to topical dermatologic preparations and orally administered antihistaminic drugs, allergic management was instituted immediately. This included procedures for the avoidance of suspected inhalant allergens, trial elimination diets, and hyposensitization injections to house-dust, grass, and ragweed-pollen extracts. The patient rapidly improved, and within a few months active cutaneous lesions regressed and nasal symptoms were only minimal. He remained asymptomatic until the following August, when there was a mild increase in nasal symptoms, with a reappearance of active dermatitis on the neck, face, forearms, and lower legs. Because of the prominent localization of the erythematous, papular, lichenified lesions on the exposed portions of the body the possibility of a contact factor was suspected. Among the patch tests performed ragweed-pollen oil was included, and this resulted in a 3+ reaction within 24 hours. The following winter, injections of ragweed-pollen oil were included in the above described regimen. On this therapy marked and progressive improvement was noted. During the past two summers, there were only very minimal seasonal nasal symptoms. Following the addition of ragweed-pollen oil with the saline-ragweed-pollen extract to his hyposensitization program he was free of symptoms of dermatitis of both atopic and contact distributions during the months of August and September.

CASE 2.—A 26-year-old white, male, train brakeman, residing in Pennsylvania, was first seen in October, 1956, after a seasonal flare-up of recurrent dermatitis that had been present since childhood. Until the age of 18 he had been subject to a mild recurrent dermatitis with limited localization to the flexor surfaces of the elbows. The eruption was perennial in occurrence but generally more prominent during the late summer months. In 1948, at the age of 18 and after he entered the Navy, the eruption spread to involve the face and neck. He was then granted a medical discharge when a positive patch-test reaction was elicited upon application of a sample piece of his blue woolen uniform. Within three to four months after his return home the dermatitis regressed and again remained localized to the antecubital areas. Two years later he entered the Army, and, while in service in Kentucky, during September, he experienced another severe flare-up of the dermatitis with a generalized distribution. He was subsequently granted a medical discharge and returned to his home in Pennsylvania in 1951. Since that time his symptoms of dermatitis essentially followed the same recurrent pattern. During the winter months he experienced an almost constant pruritic, erythematous, and lichenified eruption of the forearms and antecubital fossae, with marked generalized "skin dryness and scaling." Toward the end of each August and lasting until the late fall months he would note severe acute exacerbations of a superimposed active eruption involving the ankles, lower legs, wrists, hands, face, eyelids, ears, and neck, with sparing of the trunk. He was unable to relate precipitation or aggravation of dermatologic symptoms to exposure to any known inhalants, foods, or contactants. He stated that two years previously he received skin tests and was found to have positive reactions to "house dust, animal hairs, pollens, and a few foods." He then received "dust injections" for the next two years, without any apparent beneficial effect on symptoms related to the seasonal dermatitis. There were no associated symptoms of seasonal or perennial rhinitis, asthma, urticaria, or food intolerances. In 1951, he experienced a dermatitis after the administration of penicillin, but there was no other known history of drug reactions. The systemic review was otherwise negative. The family history was positive for allergy in that his mother had allergic asthma and a brother had eczema.

The only positive physical findings were related to the skin, which exhibited a diffuse dermatitis involving the face, neck, hands, lower legs, forearms, and flexor aspects of the elbows. This was characterized by erythema, lichenification, excoriations, and some exfoliation. There was an associated generalized white type dermatographism. The remainder of the complete physical examination findings were within normal limits.

Routine laboratory studies, including complete blood cell count, sedimentation rate, and urinalysis, were within normal limits.

Skin Tests.—On intracutaneous testing there were moderate-to-marked positive immediate wheal type reactions noted to dog hair, house dust, feathers, horse hair, rabbit hair, wool, chocolate, chicken, lamb, oats, egg, pork, rice, spinach, yeast, and ragweed-pollen extract. On patch-testing there were moderate 3+ delayed type reactions noted to the application of nickel sulfate, ammoniated mercury, and the acetone-soluble fraction of ragweed pollen (ragweed oil).

Experimental

Immunizations.—Series of adult male rabbits were each immunized with one of the ragweed antigens described below and prepared from the pollen of short ragweed, Ambrosia elatior.

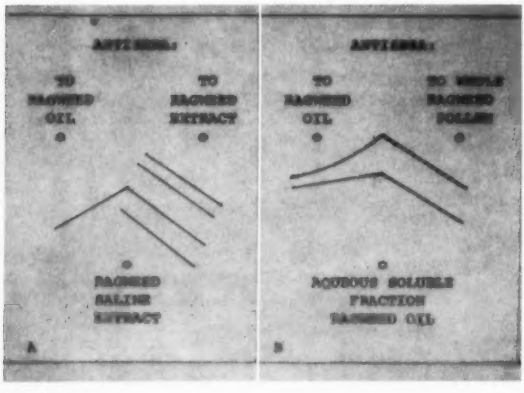
(1) Pollen Extract: A conventional type aqueous extract was prepared from ether-treated ragweed-pollen grains. Accepted methods of extraction were employed with use of an alkaline saline fluid (Coca) and glycerin. This preparation was typical of those used in the hyposensitization of ragweed-sensitive patients for treatment of rhinitis and asthma. Each animal received a total dosage of 15 mg. of protein nitrogen through a series of 12 alternating intravenous and subcutaneous injections administered in equally divided doses over a 21-day period. Antiserum was prepared from blood drawn by cardiac puncture seven days after the last injection.

(2) Pollen Oil: After pollen was defatted with ether, the ether-soluble portion was filtered off and the ether allowed to evaporate and the residual pollen oil was added to liquid petrolatum (Albolene). Each rabbit received a quantity of pollen oil recovered from 15 grams of whole pollen grains and brought up to a total volume of 16 ml. with liquid petrolatum. This was administered through a series of four alternating intraperitoneal and subcutaneous injections of 1 ml. each per week over a total period of four weeks. Antiserum was prepared from the blood drawn by cardiac puncture seven days after the last injection. The development of cutaneous sensitivity to pollen oil was determined by the appearance of a localized area of cutaneous erythema 24-48 hours after the application of the pollen oil in acetone to a shaved area on the back or flank. Such criterion was noted in only one of four treated albino rabbits of the New Zealand strain at the end of the four-week experimental period.

(3) Whole Pollen Grains: A suspension of untreated whole pollen grains (in an amount calculated to contain 15 mg. of protein nitrogen) in aluminum hydroxide cream was administered to each animal by intramuscular injection at multiple sites on the same day. Antiserum was prepared from the blood drawn by cardiac puncture 21 days later.

Precipitin Tests.—In vitro test procedures with soluble ragweed antigens and rabbit antisera to ragweed for determination of precipitin reactions were carried out in agar-filled Petri dishes according to the double-diffusion technique described by Ouchterlony.[5] In this procedure the soluble antigen and the antiserum are instilled in oppositely placed wells within the agar. Both the antigens and antibodies diffuse through the gel from opposite directions, and when they meet in suitable proportions a visible band of precipitate forms for each specific antigen-antibody system. This allows for the resolution of each antigenic preparation into individual antigenic components and each antiserum into its constituent antibodies.

The results of these tests are summarized in the Table.



Diagrammatic reproduction of precipitin reactions occurring in an agar-gel plate by the double-diffusion technique of Ouchterlony, by use of the following tests: *A*, a saline-pollen extract and two rabbit antiserums, (1) to the ether-soluble fraction of ragweed-pollen grains ("pollen oil") and (2) to a saline-pollen extract. *B*, the aqueous fraction of a water-treated ragweed oil-in-water suspension and two rabbit antiserums, (1) to the ether-soluble fraction of ragweed-pollen grains ("pollen oil") and (2) to raw intact pollen grains. The coalescence of lines of precipitate (reactions of identity) indicates the presence of common components.

Results of Tests

Antigen	Reaction	Antisera	Individual Bands of Precipitate, No.	Reactions of Identity
Ragweed saline extract	1	Antiserum to ragweed extract	4	One band in Reaction 1 coalesced with band in Reaction 2 (Fig. *A*)
	2	Antiserum to ragweed pollen oil	1	
Aqueous fraction of water-treated ragweed-pollen oil (oil-in-water suspension)	1	Antiserum to intact ragweed pollen grain	2	Both bands of precipitate in Reactions 1 & 2 demonstrated coalescence (Fig. *B*)
	2	Antiserum to ragweed pollen oil	2	

Comment.—These results indicate (1) that at least one antigenic component common to both the water-soluble and ether-soluble (oil) fractions of ragweed pollen is present and (2) that two water-soluble antigenic components of the raw ragweed-pollen grain may be carried over into ragweed "oil" during the process of ether fractionation.

Comment

Both of the patients whose case histories are reported here presented sufficient evidence to fulfill the criteria required for establishing the diagnoses of both atopic dermatitis and contact dermatitis, with ragweed pollen implicated as the causative allergen in each instance. The association of morphologically distinct types of sensitization dermatitis, existing in the same person, is not an unusual clinical observation. This may be due to independent etiologies, such as that of the delayed-contact sensitivity reaction to nickel often seen in the allergic person with atopic dermatitis[6] associated with immediate wheal type reactions of reaginic sensitivity to a variety of food and inhalant allergens, or, on the other hand, only one allergenic agent, such as paraphenylenediamine, may be the responsible etiologic factor for each, with the resultant type of dermatitis dependent upon the route of clinical exposure.[7]

The ragweed-pollen grain is a complex antigen. Its essential components are an inner core, containing the water-soluble protein fractions responsible for the syndromes of seasonal rhinitis-asthma-eczema with exposure through the inhalant route, and an outer portion, containing the oil-soluble constituent responsible for the production of dermatitis in specifically sensitized persons on direct external contact. These components are apparently unrelated, and each is considered to possess distinct biochemical and immunologic identity. Questions regarding pollen sensitization in the two patients reported here are then concerned with the underlying immunologic mechanisms. It is possible that these clinical manifestations of both the immediate reaginic and the delayed types of hypersensitivity reactions were somehow related. On the other hand, they may have been etiologically distinct and occurred in the same allergic patient only by chance.

In the case of certain foods, drugs of plant origin, animal products, metal salts, and organic compounds, Mayer[8] has noted that the same agent is capable of producing allergy of the urticaria-asthma-dermatitis group with humoral antibodies when introduced into the body by inhalation, injection, or ingestion or of the contact type dermatitis with sessile antibodies following direct skin contact. Such differences in response are attributed to chemical differences in the fibrous and globular body protein constituents to which these haptens may attach to form different and complete antigens. It has also been shown that once skin sensitization had been established to such drugs as sulfonamides[9,10] and antihistaminics[11] exacerbations of dermatitis could be elicited by either topical application or oral administration. Some patients, sen-

sitized topically to an antigenic protein agent, such as penicillin, may manifest reactions on systemic administration,[12] and both the positive immediate wheal and delayed patch-test responses have been noted in a few instances of penicillin contact dermatitis.[13,14] Whether or not the relationship of atopic dermatitis and contact dermatitis in the same ragweed-pollen-allergic patient may bear any resemblance to the clinical sensitivity states described above is not apparent.

In consideration of the possibility that both contact and atopic sensitization might have been mediated by related ragweed antigens, techniques involving experimental sensitization were attempted. Circulating precipitating antibody against one major antigenic component of the water-soluble fraction of ragweed pollen was detected in the sera of rabbits immunized with the ether-soluble fraction of the pollen grain ("pollen oil"). This finding was unanticipated, in view of the accepted concept of the selective role of proteins and carbohydrates as antigens required for the production of anaphylactic type antibody in immunologic phenomena. It was also noted that the presence of this serum antibody was not dependent upon the associated development of cutaneous contact sensitivity to the ragweed oil. Since antigenic constituents of pollen oil were shared in common with aqueous pollen extract and could be further removed from the oil by water treatment, two possible explanations are suggested: 1. The constituent is in reality a protein soluble in ether because of technical inability to extract pollen grains in a completely anhydrous state, with resultant solution of this water-soluble antigen in a water-ether colloidal suspension. 2. The constituent may be a lipoprotein, soluble in either saline or ether. However, it has thus far been impossible to identify it as such by selective precipitin band-staining in agar with lipoprotein stains.[15] The possibility of a common antigen being present in both ragweed aqueous extract and pollen oil may help to explain such unusual findings as an associated positive intracutaneous wheal-test reaction to aqueous pollen extract in patients with contact dermatitis due to ragweed oil[3] and the positive delayed patch-test reaction to aqueous ragweed-pollen extracts and albumin.[16,17]

Experimental studies have indicated the complex nature of the ragweed-pollen grain as a particulate antigen, the multiplicity of individual antigenic components, and the highly variable nature of the immune response evoked by these pollen preparations.[18] Thus, variations in clinical patterns of ragweed-pollen allergy may possibly be explained by sensitization reactions to individual pollen components in different persons. The exact immunologic basis for the presence of both immediate and delayed types of cutaneous sensitization to fractions of ragweed pollen in the same patients is not apparent. However, the fact that these two dermatologic manifestations may coexist might explain reasons for therapeutic failures of antiallergic management in some patients where the application of incomplete diagnostic measures have resulted in incomplete immunologic coverage in hyposensitization techniques.

Summary

Reports of two cases of seasonal dermatitis with unusual features are presented. Each of the patients presented typical findings of both atopic dermatitis and allergic contact dermatitis, and, in each, immediate intracutaneous wheal reactions to the aqueous extract and delayed patch-test reactions to the oil fraction of ragweed pollen were demonstrated.

Series of rabbits were each immunized with either aqueous ragweed-pollen extract or the ether-acetone-soluble oil fraction of the pollen grain. The resultant antisera were employed in precipitin-test techniques in an attempt at antigenic analysis of the ragweed-pollen components.

Ragweed-pollen oil was found to contain two constituents capable of evoking an immune response characterized by the development of circulating precipitating antibody, and this was unrelated to the development of a delayed type of cutaneous sensitivity reaction in the experimental animal. The oil constituent demonstrated evidence of immunologic identity with one of the antigenic components of the aqueous pollen fraction.

Possible explanations for these experimental findings and their clinical implications related to the dual immunologic mechanisms of immediate and delayed types of cutaneous hypersensitivity existing in the same patients are discussed.

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Superficial Epitheliomatosis Involving Intact Skin Graft

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Involvement of skin grafts by epithelioma of various types is apparently not rare. However, a rather extensive review of the literature reveals no reported cases of involvement of a skin graft by extension onto its surface without disruption of the graft. As the following case does illustrate this phenomenon, it is thought to be of reportable interest.

Report of a Case

The patient, a 45-year-old white woman, was first seen in the Dermatology Clinic, Brooke Army Hospital, on Sept. 28, 1948. At that time she had two lesions involving the temple area just lateral to the right eye and the right upper lid. She stated that previous histological studies had revealed basal-cell epithelioma. A complete work-up revealed that on Jan. 9 and Jan. 15, 1945, she had received 350 r in air to each of these two areas. On Feb. 8, Feb. 21, and March 7, 1945, she had received 350 r in air to a 2×1 cm. area lateral to the right eye by a different physician. On July 9, 1947, a bean-sized area over the central portion of the right upper lid was treated by electrodesiccation and curettement, and verrucous lesions lateral to the right eye were treated in similar manner.

At the time the patient was seen in this clinic there was marked atrophic scarring of the right upper lid and adjacent skin. Atrophy and telangiectasia were present lateral to the right eye. There was no evidence of epithelioma at that time.

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From the Dermatology Service, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

Figure 1

Fig. 1.—Photograph taken Sept. 13, 1957, at the time of treatment and biopsy, showing the involvement of both intact skin and graft. Evidence of chronic radiodermatitis can be seen, particularly at the lower border of the graft.

Figure 2

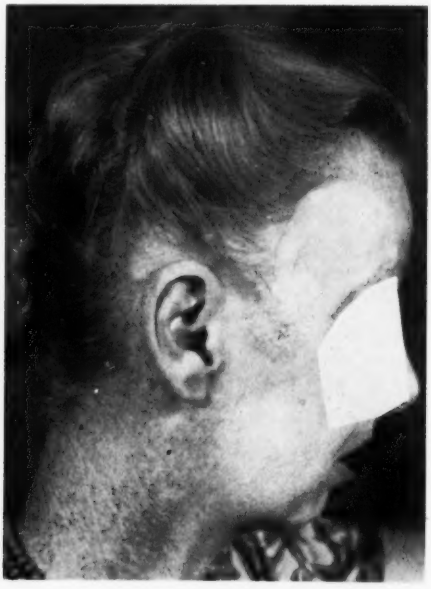

Fig. 2.—Photograph taken March 28, 1958, showing result of treatment.

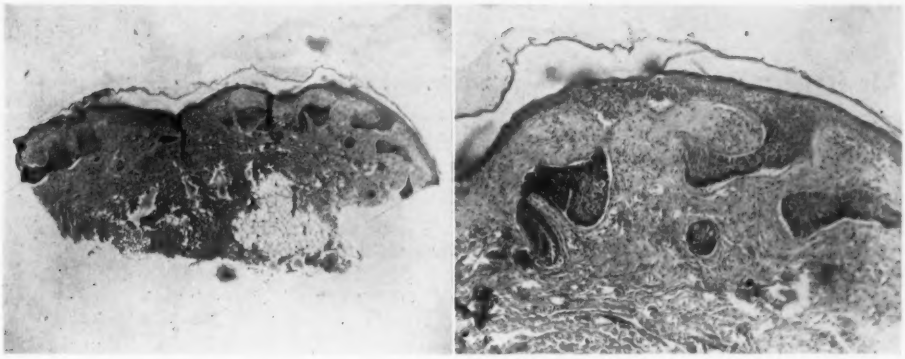

Fig. 3.—Photomicrographs revealing distinct demarcation of skin graft, which is intact, and surrounding skin. Both show typical areas of superficial epitheliomatosis. Subsequent biopsy of this area revealed complete absence of activity, with the skin graft retaining its intact character.

However, in February, 1949, there was evidence of definite activity at the margin of the scar, lateral to the right eye. Subsequently this area was treated with interstitial radium in the form of six 10 mg. radium needles with 0.5 mm. platinum filter for two and one-half hours.

During the next two years recurrent lesions of the above areas were treated with various modalities; however, the lesions continued to recur. In January, 1952, it was decided that this patient would benefit by excision and grafting of the area of repeated recurrences and chronic radiodermatitis.

This was done in February, 1952, and a split-thickness skin graft was obtained from the patient's abdomen and implanted in the area of excision. The result was satisfactory, and the patient did well until December, 1953, at which time a small scaling lesion was noted just medial to the graft. This was treated by electrodesiccation and curettement. No biopsy was done at that time.

On Aug. 29, 1957, the patient was seen for evaluation of a scaling lesion at the lower lateral border of the previously described skin graft. This lesion involved not only the surrounding tissue but was seen to extend onto the surface of the graft (Fig. 1). After careful shave biopsy the area was desiccated and curetted.

The pathology report confirmed the clinical impression of superficial epitheliomatosis. The photomicrographs revealed easy differentiation of the graft and intact skin, showing typical areas of superficial epitheliomatosis of both (Fig. 3).

Figure 3, right, shows a higher magnification of one area of involvement.

Comment

As no reports of extension onto the surface of a skin graft by any form of basal-cell epithelioma could be found, such a case is reported. This case represents a long-standing superficial epitheliomatosis which was treated by every conceivable means, including various forms of irradiation. Finally skin grafting was resorted to, with resulting invasion of the graft from surrounding remaining active lesions.

This case is thought to be of interest not only because of its unusual occurrence but it should be of particular interest to those who feel that superficial epitheliomatosis is of unicentric, rather than multicentric, origin.

Multiple Progressive Vascular Hamartomata of the Leg Simulating Kaposi's Hemorrhagic Sarcoma

Report of a Case

DESIRE J. A. REBELLO, M.D., and JAMES K. LOUTZENHISER, M.D., Cincinnati

The term hamartoma refers to benign tumors of embryonal origin. It designates tumor-like malformations showing a faulty mixture of the normal components of the organ in which they occur. The pattern and arrangement of these normal cells do not conform to the structural organization of the organ affected. The tumor is usually encapsulated. It is the disorganization, overgrowth, and encapsulation of these masses which makes them anomalous.[1] Hamartomata may occur in any organ of the body but are commonest in the spleen, liver, kidney, lung, and pancreas. In the skin they may be recognized as vascular hamartomata.

Several syndromes have been described in which vascular hamartomata of the skin are associated with visceral lesions. In Maffucci's syndrome vascular hamartomata are associated with phlebectasia, enchrondromata, dyschrondroplasia, and "spider hands." Sturge-Weber syndrome[2] consists of nevus flammeus in the distribution of one or more branches of the trigeminal nerve, glaucoma, contralateral hemiparesis, epilepsy, mental retardation, and cerebral calcification. The Parkes Weber syndrome[3] is hypertrophy of a limb due to congenital hemangiectasia. Klippel-Trénaunay disease (nevus varicosus osteohypertrophicus)[4] is composed of systematized angiomata, particularly nevi flammei, associated with varicosities and hypertrophy of the bones of the extremity in which the vascular lesions are present; secondary gigantism occasionally occurs on the opposite side. Von Hippel-Lindau's disease[5] is a familial disorder, characterized by angiomatosis and gliomatosis of the retina and cerebellum. Cysts are found particularly in the cerebellum but also in other parts of the brain, including the meninges and spinal cord. Cysts may also be found in the pancreas and kidney; so may angiomas. There are no cutaneous lesions.

The blanket term ectoneurodermal hamartomata[6] has been suggested for Sturge-Weber syndrome, Klippel-Trénaunay disease, von Hippel-Lindau disease, and Parkes Weber disease because of the difficulty in distinguishing them clinically. The term phakomatoses[7] has also been used. This includes Bourneville's disease (tuberous sclerosis), von Recklinghausen's disease (neurofibromatosis), von Hippel-Lindau disease, Sturge-Weber disease, and Klippel-Trénaunay disease. Bourneville's disease[8] may be associated with angiomata of the skin and other organs. An increased oxygen content of the peripheral vessels and higher skin temperatures are found in the affected parts in these syndromes.[6] The vascular lesions are radiosensitive, and this distinguishes them from simple nevus flammeus.[6]

Report of Case

An 11-year-old white girl was admitted to Cincinnati General Hospital for the first time in August, 1955, for multiple asymptomatic bluish lumps, distributed in a linear fashion along the inner aspects of the left foot and leg. She had similar lesions in the left inguinal area and about the umbilicus. These were not present at birth.

Submitted for publication July 2, 1958.

From the Department of Dermatology, College of Medicine, University of Cincinnati.

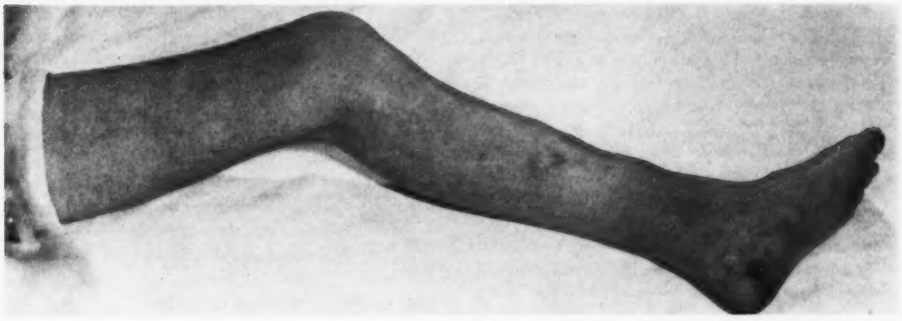

Fig. 1.—Left leg and foot, showing vascular hamartomas.

She stated that they developed gradually during the preceding two and one-half years. The first "lump" was noticed on the middle of the left leg after an injury. She stated that some of the other lesions appeared at sites of trauma. Her family history revealed that there were eight siblings, all living and well. Her father was hospitalized for a pulmonary infarction. Her past history revealed that she had had chicken pox, measles, and mumps and had sustained a skull fracture in 1952. Systemic review was noncontributory. Physical examination revealed normal pulse, temperature, and respirations. Fundus examination findings of the eye were normal. No abnormalities were detected in the chest or abdomen. Neurologic examination revealed no abnormal reflexes. There were soft, nontender, bluish nodules, 0.5 cm. to 2.0 cm. in diameter, on the left lower leg and foot. These lesions were distributed in a linear pattern along the inner aspect of the left lower extremity. The lesions on the leg were deep; those of the foot had a whitish appearance and seemed superficial but still were under the fascia. Similar nodules were present in the left inguinal area and about the umbilicus. The size of the affected leg, as compared with the other, was not commented on by any observer. In spite of the rarity of Kaposi's hemorrhagic sarcoma in children, this diagnosis was believed most likely because of the continued spread and progression of the bluish lesions. Malignant melanoma was also considered.

The hemogram and urinalysis were normal. X-ray of the left leg revealed a normal tibia and fibula; soft tissue nodules were noted, but no calcifications were seen. No soft tissue nodules or bone deformities were seen in the left foot. Skull x-ray was normal, as was the skiagram of the pelvis and lumbosacral spine. Excisional biopsies were performed by Dr. R. M. Vetto, of the Surgical Department, of the umbilical and left inguinal nodules and of four superficial nodules on the left foot, one of which was a protruding purplish nodule on the left heel. Three lesions on the left leg were also excised. The nodules of the left foot and leg followed the course of the saphenous vein and were intimately connected to tributaries of that system. One nodule was attached directly to the saphenous vein. Histopathological examination of every lesion revealed a fibrous stroma in which were interspersed numerous endothelial-lined spaces, many of which contained blood. Some of the spaces showed thrombosis and partial organization.

This patient was readmitted to the hospital on Jan. 13, 1958, because of a recurrence of some of

Fig. 2.—Infrared photography, showing relation of venous radicles to lesions.

these nodules. Physical examination was negative except for arachnodactyly, an apparent shortening of the left leg, and multiple soft, bluish nodules on the inner aspect of the left leg and foot. The shortening was not confirmed by actual measurements. A large purplish, protruding nodule was present on the left heel. Hemogram and urinalysis were again normal. X-rays of both lower extremities revealed normal bone structure; x-rays of the upper extremities were also normal. However, multiple calcific densities were seen in the soft tissues of the left leg. Several of these densities were linear in form, with track formation resembling calcifications within blood vessels. A venogram of the left lower extremity revealed an adequate and patent deep venous system. There was attenuation of the anterior and posterior tibial veins. The contrast medium filled the hamartomata of the leg. Intradermal snake-venom tests for capillary fragility were negative. Infrared photography of the legs showed the connection of the nodules with venous radicles. Dr. B. N. Carter Jr. excised all the visible nodules with their venous radicles under tourniquet. Histopathological examination revealed that these nodules were composed of vascular channels, varying in size and in some cases underlying the skin. The areas surrounding many of these vascular channels were highly cellular. A marked amount of fibrosis was noticed in areas. Focal collections of bluish-staining fragments of material were seen in other areas. These represented calcium deposits. Focal thromboses were also noted.

This patient then had only vascular hamartomas in the skin. Vascular hamartomas

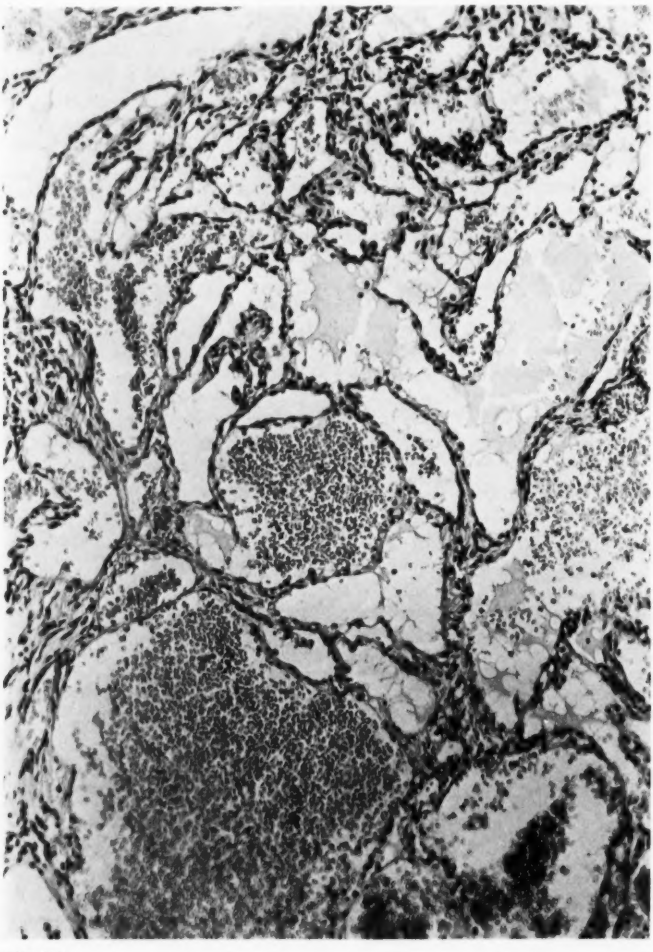

Fig. 3. — Photomicrograph of section of one of the nodules, showing endothelial-lined spaces with blood cells; reduced 10% from mag. × 160.

are poorly demarcated as a rule. Intimate mingling of the superfluous vessels with the normal tissues may give a false appearance of invasive infiltration. Moreover, the occurrence of multiple vascular hamartomas in several tissues may simulate metastases. This finding in adults must make one suspect angiosarcoma.[8]

Summary

An 11-year-old girl showed progressive development of multiple vascular hamartomata confined to one extremity. No endochondromata, visceral, intracranial, or retinal lesions were detected clinically or radiologically. She manifested only arachnodactyly. There was no hypertrophy of the affected extremity.

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Digital Blood Flow Rates in Lupus Erythematosus

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In the medical literature of this century, many authors have discussed the relationship of chronic discoid lupus erythematosus to systemic lupus erythematosus. The expressed viewpoints range from that of Belote,[1] who considered chronic discoid lupus erythematosus a variant of systemic lupus erythematosus, to that of Baehr,[2] who considered chronic discoid lupus erythematosus and systemic lupus erythematosus alike in name only.

In 1950, Huff, Taylor, and Keys[3] stated, "Chronic discoid lupus erythematosus is accompanied by pathologic changes in arteries at some distance from the lesion." These investigators claimed that an abnormal circulation exists in the fingers of patients with chronic discoid lupus erythematosus. They were uncertain whether the altered digital blood flow was due to changes in elasticity in the arterial tree or whether it was due to abnormal activity of arteriovenous shunts. In their study of 11 patients with chronic discoid lupus erythematosus, the plethysmographic tracings of the digital pulse revealed a prolonged crest time and obliteration of the dicrotic notch.

The present study was designed to compare the minute-volume flow of blood in the digits of subjects with chronic discoid lupus erythematosus and systemic lupus erythematosus and of healthy adults, under normal conditions and in response to local mild ischemia. A venous occlusion plethysmograph was used to determine the blood-flow rates. This method measures the rate of increase in finger volume when the veins are suddenly occluded, but the arterial inflow is left relatively undisturbed. Hence, for a short period of time, the minute-volume flow of blood into the finger is reflected in the rate of tissue volume increase. The equipment used was adapted from that described by Burch[4]; cuff pressures and finger volume changes were detected by Statham strain-gauge transducers and registered on a Sanborn Twin-Viso recorder.

Fig. 1.—Laboratory adjoining controlled-temperature room. *A*, Sanborn Twin-Viso recorder. *B*, hydraulic controls for calibration of plethysmograph. *C*, air-pressure controls. *D*, room-temperature control panel. *E*, viewing window.

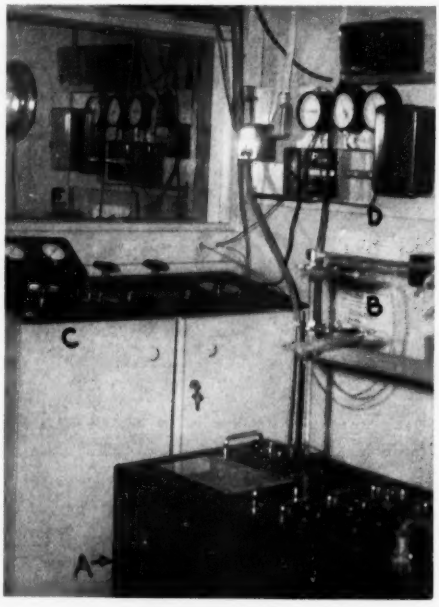

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Fig. 2.—Plethysmograph sealed to distal interphalangeal joint of index finger. Cuff for occluding the circulation is on the proximal phalanx. Airway from cup is connected to a Statham strain-gauge transducer. The cuff is inflated from a large air tank in which the pressure is regulated.

Experimental Procedures and Methods

The experiments were conducted at 30 C in a controlled-temperature room, regulated in the range of ±0.5 C. The subjects were isolated from the investigators, but visual and auditory contacts were maintained by means of a one-way viewing glass and an intercommunication system. Electrical, hydraulic, and air-pressure control systems required for making the digital blood-flow measurements were mounted outside of the constant-temperature room (Fig. 1).

All experiments were carried out in the morning between the hours of 9 and 11 o'clock. The subjects fasted for at least 12 hours prior to examination. No coffee, tea, tobacco, or medications were taken during this period. A medical history, which included a record of smoking, recent medication, and time of the last meal, was taken. The subject was then clothed in a light hospital gown and rested supine on a bed in the constant-temperature room.

A plethysmograph cup was sealed to the distal interphalangeal joint of the left index finger with a soft, rapidly setting, dental-impression plastic* (Fig. 2). The digit was then placed in a comfortable position at heart level. Pressure changes in the plethysmograph cup were transmitted by an airline of low distensibility to a Statham P23B strain-gauge transducer (Fig. 3) and transcribed by the Sanborn Twin-Viso recorder. The volume calibration of the plethysmograph was accomplished at the end of each experiment by occluding all blood flow to the digit with a brachial cuff. While the circulation was interrupted, 10 cu. mm. of air was introduced into the cup by means of a Grass calibrating unit. The maximum sensitivity of the system ranged from 6 to 9 mm. of stylus deflection per 10 cu. mm. of volume change, depending on the ratio of the plethysmograph volume to finger volume.

* Sili-Gel, made by the Dental Perfection Company, Glendale, Calif.

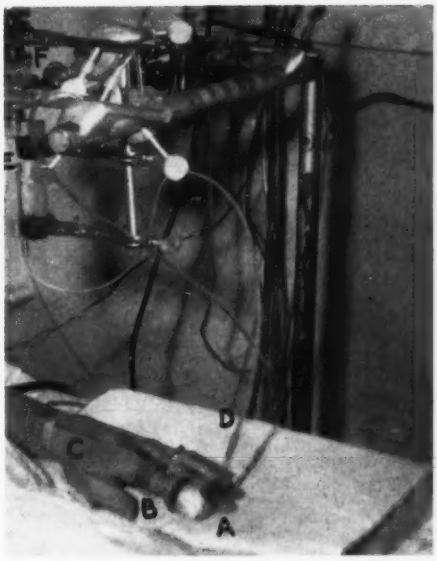

Fig. 3.—Controlled-temperature room. *A*, plethysmograph. *B*, digital pressure cuff. *C*, airway from cuff to pressure tank via strain gauge transducer. *D*, airway from plethysmograph to strain gauge transducer. *E*, Grass calibrating unit. *F*, strain-gauge transducer for plethysmograph. *G*, second transducer for cuff pressure measurement.

Instantaneous venous occlusion was effected by use of a direct-contact rubber cuff fashioned from $^3/_{16}$ in. Penrose drainage tubing which was inflated from a large air tank in which the pressure was regulated. The cuff was placed on the proximal phalanx of the left index finger. This arrangement was found to produce no appreciable distortion of the plethysmographic record and provided a high degree of reproducibility of blood-flow measurements. Inflation and deflation of the digital cuff were controlled by remotely operated solenoid valves. Collecting pressures of 10 to 20 mm. of mercury below the diastolic brachial pressure have generally been found to be adequate for making digital blood-flow measurements. Venous occlusion pressures of 50 to 60 mm. of mercury were used most frequently. Changes of collecting pressure in the range of 40 to 70 mm. of mercury produced no apparent change in blood-flow readings in the majority of subjects.

The subject was isolated in the dimly lighted room and allowed to rest for 10 minutes. A series of 6 to 10 resting blood-flow measurements was then made at two-minute intervals. An interval of two minutes was allowed between successive occlusions of the venous circulation in order to avoid

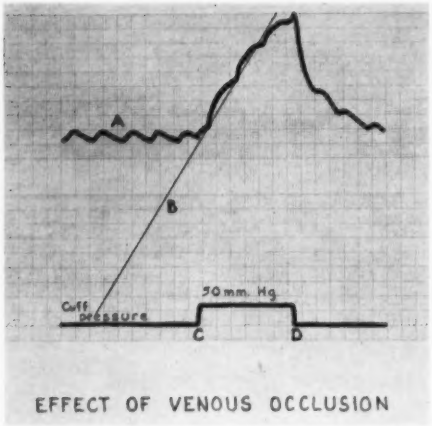

Fig. 4.—Typical digital blood-flow measurement. *A*, digital pulse waves prior to venous occlusion. *B*, slope indicating rate of filling of finger. *C*, point of instantaneous venous occlusion. The cuff pressure is 50 mm. Hg. *D*, release of cuff pressure. Finger volume returns to the control level.

errors associated with passive congestion or reflex changes in vasomotor tone resulting from the previous application of pressure to the digit. The blood-flow rate was determined from the average change of rate in finger volume recorded during the first complete pulse beat after venous occlusion (Fig. 4). Occlusion of the digital veins was effected during the last 0.1 to 0.3 sec. of the diastolic phase of the preceding pulse cycle. This was done in order to minimize filling of the vascular reservoir prior to measurement of the flow rate. After measurement of the resting blood-flow rates, the effect of local mild ischemia on the digital minute-volume flow was tested. The pressure in the finger cuff was suddenly raised to 200 to 280 mm. Hg and maintained at this level for three minutes. At the end of this time, the rate of blood flow into the finger was determined by sudden lowering of the cuff pressure to a level sufficient to sustain the venous occlusion (Fig. 5). After a period of 10 minutes, the digital circulation was occluded a second time for 5 minutes. The rate of blood flow in the reactive hyperemic phase was again recorded in the manner described.

At the conclusion of the experiment, the volume of finger enclosed within the plethysmograph was determined. While the finger was still in place, a measured volume of water was injected into the cup by means of a hypodermic syringe equipped with a short length of polyethylene tubing. The volume of water injected was then subtracted from the volume of the cup, which had been previously measured.

The values obtained for minute-volume blood flow in this laboratory are of the same order as those reported by Burch [4] and Burton.[5]

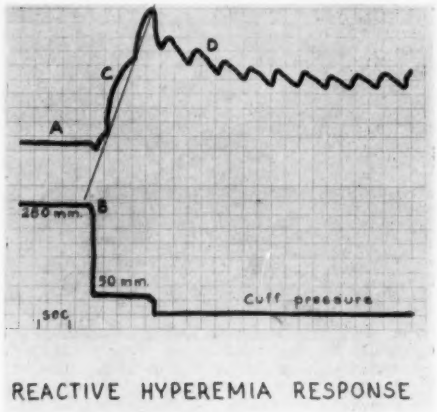

Fig. 5.—Typical measurement of the digital blood flow during reactive hyperemia: *A*, circulation occluded for three minutes by raising pressure in the digital cuff to 280 mm. Hg. *B*, point of release of finger-cuff pressure from 280 mm. Hg to 50 mm. Hg (arterial occlusion ends; venous occlusion persists; finger fills with blood). *C*, first complete pulse wave after restoration of the circulation. *D*, pressure in digital cuff released.

Clinical Material.—Digital blood-flow measurements were made in 79 subjects, comprising control and patient groups. They were classified according to sex, age, and disease. A summary of the number of subjects studied in each group appears in Table 1.

Results

Clinical Diagnoses.—The clinical findings in 10 males and 13 females with chronic discoid lupus erythematosus are summarized in Tables 2 and 3 respectively. The age of the patients in these two groups ranged from 31 to 70 years. None had elevation of the systolic or diastolic arterial pressure; none was febrile at the time of

TABLE 1.—*Number of Subjects Studied According to Age, Sex, and Disease*

	Males		Females		
		Chronic Discoid		Chronic	
Age Range	Control	L. E.	Control	Discoid	Systemic
20-30	7	0	15	0	4
31-40	5	2	5	8	3
41-50	5	3	5	2	0
51-60	1	1	3	2	0
61-70	2	4	1	1	0
Total	20	10	29	13	7

TABLE 2.—*Clinical Findings in Male Patients with Chronic Discoid Lupus Erythematosus*

Case	Age	Duration, Yr.	Areas of Involvement	Recent Treatment
1	31	1	Face, neck	Chloroquine
2	38	4	Red macular face	None
3	41	4	Nose, forehead	Chloroquine
4	44	20	Cheeks & ears with scarring	None
5	47	6	Shoulders, chest	None
6	60	30	Scars on face	None
7	62	8 mo.	Cheeks, nose, arms, chest	Cortisone
8	63	3	Red plaques, face	Chloroquine
9	70	10	Atrophic plaques, chin & scalp	None

examination. Diagnosis of chronic discoid lupus erythematosus was confirmed by biopsy and laboratory studies, including complete blood cell count, urinalysis, protein fractionation, etc. Most patients were receiving chloroquine 12 hours prior to the time of study; there is no evidence that ingestion of this drug affects blood flow or vascular reactivity.

The diagnosis of systemic lupus erythematosus was established by physical examination and laboratory procedures. All seven patients were females. None was febrile at the time of our investigations; none had elevated systolic or diastolic arterial pressures; all seven patients at one time or another had been acutely ill with symptoms typical of systemic lupus erythematosus. These patients were judged to be in a "subacute" phase of the disease

TABLE 4.—*Clinical Findings in Female Patients with Systemic Lupus Erythematosus* *

Case	Age	Duration	Recent Treatment	Symptoms
23	28	1	PABA	Arthralgias
24	16	6	Chloroquine (Aralen), prednisone	Arthralgias, inactive cheek plaques
25	28	6 mo.	Chloroquine, prednisone	Arthralgias, facial erythema, & pigmentation
26	33	4	Chloroquine, prednisone (Meticorten)	Inactive lesions, face, chest, & arms
27	36	4	Chloroquine, prednisone	Widespread skin lesions, arthralgias
28	23	5	Prednisone	Faint facial erythema
29	40	5	None	"Cold fingers"

* Phase of disease in all cases was subacute lupus erythematosus.

TABLE 3.—*Clinical Findings in Female Patients with Chronic Discoid Lupus Erythematosus*

Case	Age	Duration, Yr.	Areas of Involvement	Recent Treatment
10	31	1	Face, neck	Chloroquine
11	32	8	Scalp, cheeks	Chloroquine
12	33	5	Face, with erythema cheeks & lip	Chloroquine
13	34	5	Cheek, forehead	Chloroquine
14	35	9	Severe scarring entire face	Chloroquine
15	39	3	Erythema cheeks, nose, & eyelids	Chloroquine
16	39	14	Scarred lip & nose	None
17	40	5	Areas of cheeks	Chloroquine
18	49	2	Face, right arm	Chloroquine
19	43	12	Scaly red areas face	Chloroquine
20	57	3	Red plaques face & neck	Chloroquine
21	57	3	Erythema face	None
22	61	5	Face	Chloroquine

at the time of examination. Only one patient complained of "cold" fingers. Raynaud's or other vasospastic phenomena were not observed in this group. The one patient with "cold" fingers had digital blood-flow measurements on three separate occasions. There was no appreciable difference in the blood flow rate on successive examinations. None of these patients had visible cutaneous lesions on the digit studied. Clinical information concerning this group is presented in Table 4.

TABLE 5.—*Digital Blood Flow Rates in Male Subjects*

	Flow Rates, Cu. Mm/5 Cc/Sec.	
	Controls	Discoid L. E.
Control phase		
Median	30.3	29.9
Confidence intervals for the median	24.5-45.1	5.4-45.1
Confidence coefficient	96%	97.9%
Number of subjects	20	10
Reactive hyperemia phases		
Post 3-min. occlusion		
Median	55.4	35.1
Confidence intervals for the median	32.4-67.5	20.0-51.7
Confidence coefficient	97.8%	96.9%
Number of subjects	13	6
Post 5-min. occlusion		
Median	48.6	50.4
Confidence intervals for the median	41.4-64.0	19.1-62.7
Confidence coefficient	98%	96.9%
Number of subjects	9	6

Digital Blood Flow in Controls and in Chronic Discoid Lupus Erythematosus.—The values for digital minute-volume blood flow in control subjects and also in chronic discoid lupus erythematosus are presented in Table 5. Analysis of the data reveals that median values obtained in 20 control males were very similar to those obtained in a group of 10 males with chronic discoid lupus erythematosus. However, the values for the confidence intervals suggest that the flow, although similar in both groups, may have been somewhat higher in the controls. Apparent differences in the blood flow seen between the two groups in the control phase of the experiment were accentuated in the succeeding phase of reactive hyperemia induced by arrest of the digital circulation for three minutes. Although these figures suggest a real difference in finger blood flow between control subjects and patients, statistical analysis † of all the available data indicates that they could well occur solely on the basis of chance. No correlation between digital minute-volume blood flow and age could be established in these or any of the subsequent groups studied.

Minute-volume blood flow in the digits of 29 healthy females and 13 women patients with chronic discoid lupus erythematosus was found to be essentially the same during the control phase of the experiment. As indicated by the data in Table 6, the hyperemic response increased with the duration of arterial occlusion and was similar in control and diseased subjects alike after three and five minutes of circulatory arrest, respectively. No statistical difference in digital blood flow between the two groups in any of the three phases of the experiment could be demonstrated.

Digital Blood Flow in Systemic Lupus Erythematosus.—Results obtained in seven women with systemic lupus erythematosus are presented in Table 7 and included in summary form in Table 6 for purposes of comparison.

Blood-flow values in Cases 137 through 188 were considerably lower during the control phase of the experiment than were the median values obtained for both normal women and those with chronic discoid lupus erythematosus under comparable conditions.

† Significance tests are based on the Wallis-Krushal H Test, in Wallis, W. A., and Roberts, H. V.: Statistics: A New Approach, Free Press, Glencoe, Ill., 1956, p. 600.

TABLE 6.—*Digital Blood Flow Rates in Female Subjects*

	Flow Rates, Cu. Mm/5 Cc/Sec.		
		Lupus Erythematosus	
	Controls	Discoid	Systemic
Control phase			
Median	18.0	21.9	12.2
Confidence intervals for the median	12.4-27.8	4.5-35.2	1.3-23.5
Confidence coefficient	97.6%	97.8%	98.4%
Number of subjects	29	13	7
Reactive hyperemia phases			
Post 3-min. occlusion			
Median	36.3	36.9	26.0
Confidence intervals for the median	22.1-51.3	20.8-46.4	11.7-45.1
Confidence coefficient	96.9%	96%	93.8%
Number of subjects	18	12	5
Post 5-min. occlusion			
Median	40.7	39.0	25.4
Confidence intervals for the median	31.2-55.9	28.2-53.2	16.2-57.2
Confidence coefficient	96%	96%	96.9%
Number of subjects	20	12	6

TABLE 7.—*Digital Blood Flow in Systemic Lupus Erythematosus*

		Flow Rates, Cu. Mm/5 Cc/Sec.			
Case	Age	Control Phase (Median)	Post 3-Min. Occlusion (Instantaneous)	Post 5-Min. Occlusion (Instantaneous)	Remarks
137	40	1.3	13.9	18.7	"Subacute" L. E.
79	16	2.5	11.7	16.2	"Subacute" L. E.
55	28	9.6	26.0	24.7	"Subacute" L. E.
188	28	12.2		26.0	"Subacute" L. E.
179	33	21.0	37.5	34.5	Asymptomatic (normal laboratory tests)
58	23	22.6	45.1	57.2	Asymptomatic
84	35	23.5			"Subacute" L. E.

Flow rates observed after three and five minutes of arterial occlusion, respectively, were also lower. In Case 137, a 107-fold increase in blood flow occurred immediately after three minutes of circulatory arrest. After the circulation to the finger tip had been arrested for five minutes, a 14.4-fold increase in blood flow was seen. However, despite the high degree of response to local ischemia, the minute-volume flows observed in this case were still below the median values observed in female controls and in those with chronic discoid lupus erythematosus, under similar conditions (Table 6). Inspection of Table 7 reveals that similar results were obtained in Cases 79 and 55. Values obtained in Cases 179 and 58 were comparable to flow rates in control females. However, it is noted that these persons were asymptomatic at the time of examination.

Comparison of Digital Blood Flow in Males and Females.—The resting digital blood flow in male controls is significantly higher than that in female controls under similar test conditions. This is shown by the data in Tables 5 and 6. The median values for blood flow obtained in males is 30.3, whereas that for females is 18.0. The two groups of measurements are significantly different at the 1% level, by the Wilcoxon Two Sample Test.‡

Pulse-Wave Analysis.—The normal digital pulse wave consists of an ascending anacrotic limb which occurs during the systolic phase of the heart beat and a descending catacrotic limb in the diastolic phase (Fig. 6). A dicrotic notch usually occurs in the catacrotic limb. It is a negative wave associated with closure of the aortic valves and the elastic recoil of the aorta and other great vessels. Some of the factors affecting the form of the pulse wave are stroke volume of the heart, elasticity of the vessel walls, duration of systole and diastole, and pulse pressure.

According to Dillon and Hertzman,[6] the normal pulse wave has a crest time (anacrotic limb) which is 20% or less of the pulse-cycle time. Hertzman and Roth [7] found that after immersion of a limb in cold water the crest time of the digital pulse increases and the dicrotic notch disappears. Burton [5] has pointed out that the degree of fullness of the capillary and venous reservoirs may influence the form of the pulse wave.

In the analysis of the pulse-wave data, the subjects have been classified according to the characteristics of the crest time and

‡ Wilcoxon Two Sample Test, in Mann, H. B., and Whitney, D. R.: On a Test of Whether One of Two Random Variables Is Stochastically Larger Than the Other, Ann. Math. Stat. 18:50-60, 1947.

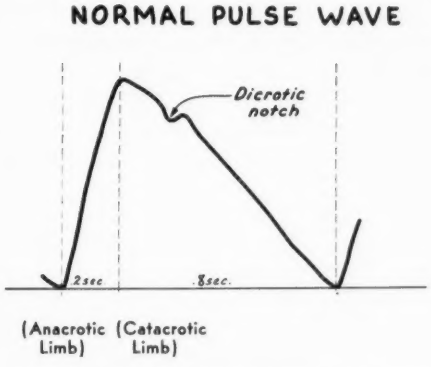

Fig. 6.—Normal pulse wave, showing rising anacrotic limb, sharp peak or crest, and catacrotic limb with dicrotic notch. Crest time corresponds with anacrotic limb.

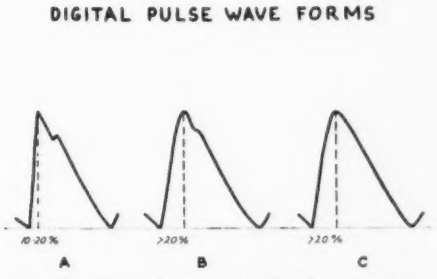

Fig. 7.—Comparison of digital pulse-wave forms predominating in this series. *A*, quick crest time and sharp dicrotic notch. *B*, slower crest time and slightly diminished dicrotic notch. *C*, long crest time and absent dicrotic notch.

the dicrotic notch which predominate throughout each tracing. Though at times a slight variation might be noted from one wave to the next, the great majority of pulse waves obtained from each subject followed the same pattern.

At least three wave forms were found to predominate in the pulse tracings studied in this series (Fig. 7).

Group A consists of tracings in which the crest time is less than 20% of the cycle time. A dicrotic notch is present. In Group B, the crest time is over 20% of the cycle time and the dicrotic notch is slightly diminished. Tracings in Group C are characterized by crest times in excess of 20% of the cycle time and the absence of the dicrotic notch. This pulse configuration, according to Huff, Taylor, and Keys,[3] is characteristic of chronic discoid lupus erythematosus. Our data do not reveal a pulse-wave configuration distinctive of either chronic discoid lupus erythematosus or systemic lupus erythematosus (Fig. 8). The results of pulse-wave analysis are presented in Table 8. Of the 79 subjects studied, 48 comprised Group A; 17, Group B, and 14, Group C.

Fig. 8.—Comparison of pulse-wave configurations in controls and patients with systemic lupus erythematosus and chronic discoid lupus erythematosus. The controls appear on the left; the patients, on the right. Both of the patients with systemic lupus erythematosus are in the subacute phase. The patient with chronic discoid lupus erythematosus has active lesions on the face. Lack of specificity of waves is quite evident. The waves at the top (No. 1) show sharp dicrotic notches and rapid crest times. The waves of the mid- and lower sets show somewhat longer crest times and depressed or absent dicrotic notches.

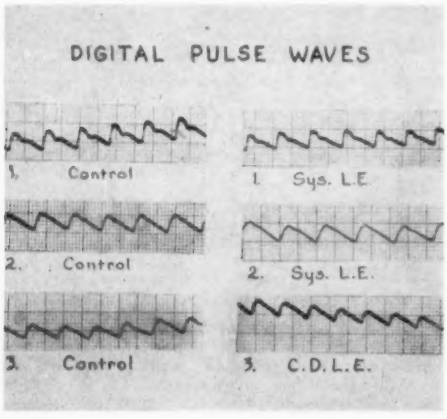

TABLE 8.—*Classification of Subjects According to Presence of Dicrotic Notch and Crest Time*

Subjects	Time Over 20% Cycle Time		
	Dicrotic Notch & Short Crest Time (Group A)	Long Crest Time & Dicrotic Notch (Group B)	Long Crest Time & Absence of Dicrotic Notch (Group C)
Control			
Males	17	2	2
Females	17	7	5
Chronic Discoid L. E.			
Males	5	4	0
Females	6	3	4
Systemic L. E.			
Males	0	0	0
Females	3	1	3

Comment

The present series of studies reveals a high degree of variability in the resting digital blood flow (control phase) in the same person and also among subjects. Burton[5] and Patel and Burton[8] have also reported highly variable resting digital blood flow, far in excess of the metabolic needs of the tissue. These authors suggested that the oscillations are mediated largely by arteriovenous anastomoses and are related to temperature regulation. Hence, the total digital blood flow, as measured by the plethysmograph, is not necessarily indicative of capillary blood flow on which nutrition of the tissue depends.

Data obtained in studies of the digital circulation in controls and patients with chronic discoid lupus erythematosus do not reveal any significant differences in minute-volume flow between the two groups. Although wide variations were seen in some cases, the differences can be explained on the basis of normal vasomotor activity in arteriovenous anastomoses and other vessels. From the data accumulated, there is no solid evidence to support the statement, "Patients with chronic discoid lupus erythematosus have a defect in the circula-

tion of the fingers."[3] Studies now in progress in our laboratory are concerned with the "effective" capillary flow in the digit rather than the total flow. It is possible that this line of investigation may reveal some defect of tissue nutrition in patients with lupus erythematosus.

The significantly lower blood-flow rates in females, as compared with males, may account for the difference between our results and those reported by Huff et al.,[3] whose control group was comprised predominantly of males, whereas the patient group consisted largely of females. Previous reference to a sex difference in digital blood flow appears to be lacking in the literature. Our finding may be related to the lower basal metabolic rate found in women, compared to men of similar body size.[9] On this basis it is to be expected that digital vasomotor tone should be higher and flow rates lower in women than in men. Since the size of the finger in which blood-flow measurements were made was corrected to a standard 5 cc. unit, differences in finger volume can be eliminated as a contributing factor. Differences in the ratio of soft tissue to bone may be involved, but an increased vasomotor tone in women, from whatever cause, is a more likely explanation.

The data in Table 7 suggest lower digital blood flows in females with systemic lupus erythematosus compared to controls, but this is not demonstrable on a statistical basis with the available data. No definite conclusions can be drawn for the group as a whole because of the small number of patients examined.

Summary

Seven women with subacute systemic lupus erythematosus, twenty-three men and women with chronic discoid lupus erythematosus, and forty-nine healthy men and women were studied to determine their digital blood flow rates under normal conditions and in response to mild local ischemia.

Four of the seven female patients with systemic lupus erythematosus were found to have an apparently diminished blood flow compared to controls of like age and sex; the differences were not statistically significant.

The blood flow of persons with chronic discoid lupus erythematosus was essentially the same as the group of controls.

There is no evidence that a characteristic pulse-wave pattern occurs in either systemic lupus erythematosus or chronic discoid lupus erythematosus.

Higher rates of blood flow were found in males than females in both control and patient groups. The differences were statistically significant.

No correlation between digital blood flow and age could be established in any of the groups studied.

Dr. Lincoln Moses aided in the statistical analysis of the data.

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ABSTRACT OF DISCUSSION

DR. LOUIS H. WINER, Beverly Hills, Calif.: It is a difficult problem for us to assure a patient that her chronic discoid lupus erythematosus is not going to become systemic lupus erythematosus. Patients have been diagnosed chronic discoid lupus erythematosus without studies for systemic lupus erythematosus having been done. These patients may have had systemic lupus erythematosus with clinical lesions simulating chronic lupus erythematosus. The changes indicative of systemic lupus erythematosus were not predominant and therefore not sought after.

For eight years we have been following a patient with disseminated chronic discoid lupus erythematosus, who has at no time shown any findings characteristic of systemic lupus erythematosus. We treated her with 1,500 to 2,000 mg. of chloroquine a day for weeks at a time, which did not alter the course of the disease. We then treated her with heavy dosages of steroids, with improvement. Histologically she has chronic discoid lupus erythematosus.

The disseminated chronic discoid lupus erythematosus can histologically resemble systemic lupus erythematosus by the presence of edema. However, the hyperkeratosis, the follicular plugging, and the epidermal and adnexal atrophy are indicative of the condition's being chronic discoid lupus erythematosus.

DR. RUDOLF L. BAER, New York: I enjoyed Dr. Farber's study very much. It is this type of objective approach which eventually will help to solve the problem as to whether the chronic form and the subacute and acute forms of lupus erythematosus basically are the same disease.

Until more such objective evidence becomes available it would be best to withhold judgment regarding a possible close relationship between the different forms of lupus erythematosus. I am thinking particularly of the recent survey of Reiches (*Ann. Int. Med.* 46:678, 1957) among dermatologists, which indicated that about 25% of those asked had observed cases where transition from chronic discoid lupus erythematosus to the systemic forms had taken place.

Furthermore, there is a recent study by Kushniruk (*Canad. M. A. J.* 76:184, 1957), who subjected 35 patients with chronic discoid lupus erythematosus to the same thorough systemic studies as are usually carried out in patients with the systemic form of the disease. He found in many of his cases such abnormalities as a moderately or markedly increased sedimentation rate, elevated temperature, migratory joint pains, Raynaud's phenomenon, or other evidence which might well be considered significant in patients with the systemic form of lupus erythematosus. The value of Kushniruk's study would have been greater perhaps if he also had studied a control series of patients with diseases other than lupus erythematosus in the same thorough manner in order to ascertain what incidence of such abnormalities they would show.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Before the days of the L. E. test, about a third of our cases of chronic discoid lupus erythematosus went into what we now call the systemic, rather than the disseminate, type. The histopathologic changes in chronic discoid lupus erythematosus develop about six weeks after the first sign of clinical eruption, but this is also true of systemic lupus erythematosus, and, contrary to what Frank Ellis has said, we cannot always be certain about differentiating histologically between chronic and systemic L. E. on the basis of skin biopsy because the histologic picture will vary depending on the age of the lesion biopsied. It is significant, now that we have the L. E. test and the L. E. phenomenon, that probably less than a third of our cases of systemic lupus erythematosus ever have any cutaneous manifestations.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I should not be getting up again, but in the old days before we had the lupus erythematosus test and the "Oxford Looseleaf Medicine" a third of our cases of chronic discoid lupus erythematosus went into what we now call the systemic rather than the disseminated forms. I also took biopsy specimens in those days, in all stages, and, contrary to what Frank Ellis would say, you cannot pick out a spot of lupus erythematosus for a biopsy specimen unless you observe the patient.

The histology in chronic discoid lupus erythematosus will develop about six weeks after the first sign of clinical eruption, but one can see histologic pictures of chronic discoid lupus erythematosus in systemic lupus erythematosus in six weeks' time. However, now we have the L. E. test, and if Louis Brunsting is here, he can tell you that probably less than one-third of our cases of systemic lupus erythematosus ever have any cutaneous manifestations whatsoever. We have to rely on the L. E. test, as well as these newer data that Dr. Farber has brought to us today.

DR. E. RICHARD HARRELL, Ann Arbor, Mich.: As our knowledge of disease increases from year to year, it is not uncommon that it becomes necessary to negate or correct findings which were considered to be truths. Such is the value of the very

excellent paper we have just heard by Dr. Farber. Essentially he has found that chronic discoid lupus erythematosus does not have a decrease in digital blood flow. Neither is there evidence that a characteristic pulse-wave pattern occurs in either systemic lupus erythematosus or chronic discoid lupus erythematosus. There have been so many attempts to make a systemic disease of the chronic discoid form of lupus erythematosus that Dr. Farber's essentially negative findings assume increasing significance. However, a very positive finding has been contributed to our knowledge of digital blood flow by this report demonstrating the very marked blood-flow differences between males and females in both the control and patient groups. With this knowledge one can readily appreciate how the original error was made in the report by Huff et al. The controls in this paper, which reported a decreased blood flow in chronic discoid L. E. were largely males, while the patients were largely females. That this difference between the sexes occurs normally in the rate of digital blood flow must be given careful consideration in all future investigative work of this type. It is interesting to speculate about the possibility that a decreased digital blood flow in females is caused by some degree of intravascular formation of red corpuscle "sludges," as was reported by Knisely and coworkers (Knisely, M. H.; Bloch, E. H.; Eliot, T. S., and Warner, C.: Sludged Blood, *Science* 106:431-440, 1948). These investigators, working on the obliquely illuminated bulbar conjunctiva, reported the intravascular agglutination of red corpuscles. They felt that this agglutination was probably based on the formation of an abnormal protein coating, making the surface of the corpuscles somewhat sticky. These agglutinated cells caused a considerable reduction in the rate of blood flow of the capillary bed. It is of particular interest that this finding was reported in half of all of the normal pregnancy patients studied. It was also present in several vascular disease states, as well as in infectious diseases.

I am sure, that with this very excellent start in the investigation of the vascular abnormalities associated with lupus erythematosus, Dr. Farber and his associates will continue to work toward furthering our knowledge of this most important disease. As a matter of fact, he has indicated to me by letter that he has done some investigation of nail bed capillary changes in chronic discoid lupus erythematosus and skin-temperature changes of the discoid lesions as well as normal skin. I would be most interested to have Dr. Farber comment on any results he might have from his unreported investigations.

DR. EUGENE M. FARBER, San Francisco: I am grateful for the lively discussion, and I shall answer first some of the points which Dr. Harrell so wisely made in regard to sludging of blood.

This is an interesting phenomenon. It is difficult to recognize sludging. The erythrocytes have a very granular appearance, and it takes a great deal of experience to be sure that sludging does occur. I am certain that in the females sludging of blood is not a factor because in digital circulation so much blood flows through arteriovenous anastomoses. The female may have a lower digital blood flow than the male because of a high vasomotor tone, which involves the arterioles and the arteriovenous shunts; their finger temperature is also lower.

In collateral studies of the nail beds of patients with chronic discoid lupus erythematosus we saw no vessel changes. There are "actual" changes in the vessels in a lupus plaque, as evidenced by plaque temperature measurements. Thermocouples were placed on a lupus plaque and on adjacent skin and on distant skin. The temperature of the room was increased and decreased; the lupus plaques were slow to cool. Apparently in the lupus plaque there is a decreased ability to vasoconstrict.

As far as Dr. Winer's remarks are concerned, I do not believe that this study is meant to be an argument that chronic discoid lupus erythematosus never becomes systemic lupus. I merely wanted to establish the point that chronic discoid lupus erythematosus should not be called a "diffuse vascular disorder." To do so confuses our thinking as far as the etiology of this disease is concerned.

The patients with so-called chronic discoid lupus, who "end up" with systemic lupus, may have been systemically ill to begin with.

Triamcinolone in the Treatment of Psoriasis

MAX R. GREENLEE, M.D., and WILLIAM L. EPSTEIN, M.D., San Francisco

Treatment of uncomplicated psoriasis with steroids in general is unsatisfactory.[1,2] Recently, however, a new corticosteroid, triamcinolone,* has been marketed and from clinical trials appears to have a dramatic effect in relatively low doses.[3-5] This remarkable observation prompted us to investigate the drug in a group of psoriatics under rigid experimental conditions.

Methods

Thirty-four patients with uncomplicated but recalcitrant psoriasis of 10 or more years' duration volunteered to be subjects.† The experimental plan called for one group to receive 4 mg. four times a day for a month; a second group, 4 mg. daily, and a third group, a placebo. All other therapy was discontinued. At the end of one month, the treatment schedule was arbitrarily changed. At random, some patients received 8 mg. daily, some a placebo, and some nothing. In the third month, all treatment was stopped and follow-up observations were made. The subjects were seen at weekly intervals.

Results

The results were clear-cut. Of 12 subjects given 16 mg. daily, 11 noted improvement within the first week of treatment. Nine evidenced 80% to 100% clearing of psoriasis at the end of four weeks despite all efforts to discourage them. Three of four subjects developed mild recurrences when the drug was reduced to 8 mg. daily. Abrupt withdrawal of the drug resulted in a temporary bout of malaise in four of eight subjects, similar to that seen with administration of other steroids.[6] In every instance the psoriatic patches promptly returned when the drug was stopped. While several subjects were alarmed at the rapidity of recurrence, none exfoliated, and all lesions eventually took on a chronic appearance.

In contrast, only 1 of the 12 subjects receiving 4 mg. daily experienced any apparent improvement. When the dose was increased to 8 mg. daily, only 2 of 7 subjects noted substantial clearing of psoriasis. As before, all gains were lost when the drug was discontinued.

Ten subjects received only placebo therapy plus encouragement. Two of these definitely improved. It seems that suggestion and encouragement alone are as effective as low doses of triamcinolone.

The undesirable effects of triamcinolone in general were proportional to the dosage.

Undesirable Effects of Triamcinolone

Daily Dosage, Mg.	Subjects	Undesirable Effects
16	12	6
8	10	3
4	12	0

These undesirable effects included palpitations, muscle cramping, excessive flushing of the face, hyperhidrosis, polyuria, dizziness, and vague epigastric distress. In three of our subjects a combination of mental depression, lethargy, and muscle cramping necessitated premature withdrawal of the drug. In each instance the symptoms subsided promptly when triamcinolone was stopped. One patient developed deep pigmentation of the exposed areas

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From the Subdepartment of Dermatology, Department of Medicine, University of California School of Medicine.

* The triamcinolone was supplied through the courtesy of Dr. John T. Groel, Associate Medical Director, The Squibb Institute, New Brunswick, N. J.

† The National Psoriasis Research Association (Diane Mullins, Pres.) cooperated in contacting potential subjects.

of the body and mild facial hirsutism while receiving 16 mg. daily. Side-effects were not related to clinical improvement. Abrupt withdrawal of the larger dosage caused temporary malaise and flu-like symptoms in four subjects.

While most corticosteroids cause salt retention and weight gain, triamcinolone has the happy faculty of producing weight loss. This is not invariable and is usually related to dosage. Our subjects receiving 4 mg. daily noted essentially no reduction in weight. The most striking correlation in the series was between initial weight and degree of weight loss on triamcinolone; the most obese subjects lost the most weight. On the other hand, weight loss was not related to clinical improvement.

Comment

Obviously, triamcinolone is a potent drug for the treatment of psoriasis. Recalcitrant psoriatic plaques disappeared in 9 of 12 subjects while they were on adequate doses. However, the drug can not be recommended for general treatment because (1) undesirable physiological effects are common and (2) psoriasis nearly always recurs when the dose is reduced or discontinued. Furthermore, any steroid administered over a long period of time may not be without danger to the patient. Nevertheless, triamcinolone should find a place in the treatment of psoriasis because in some subjects it is well tolerated and effective. It is very likely the initial steroid of choice for complicated, steroid-sensitive psoriasis. The patient's response will then determine whether or not the drug can be continued and whether or not prolonged treatment is feasible. It is conceivable that, once having cleared the subject with triamcinolone, the recurring eruption will be more amenable to treatment by conventional means.

The mechanism of action of triamcinolone in psoriasis is not clear. It is doubtful that it possesses a specific anti-inflammatory effect. Rather most authors,[3,5] including ourselves, view its unique action as due to an unusual affinity of active material for the skin. Experiments to test the validity of this notion are currently under way.

Summary

Triamcinolone is evaluated as a therapeutic agent for chronic recalcitrant psoriasis in 34 patients under experimental conditions. The results indicate that, while triamcinolone is a potent and valuable drug in the treatment of psoriasis, its value is limited because of untoward reactions encountered when effective doses are given and recurrences occur upon withdrawal of the agent.

School of Medicine, University of California Medical Center (22) (Dr. Epstein).

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Disseminated Granuloma Annulare

Report of a Case Treated with Chloroquine Phosphate (Aralen)

EDWARD H. MANDEL, M.D., New York

The literature has been reviewed, and there are no reports of treatment of disseminated granuloma annulare with chloroquine phosphate (Aralen).

The therapy of localized granuloma annulare is varied, and the response in each patient is unpredictable. A method of treatment may induce immediate clearing of the lesions of one patient, whereas the identical treatment in another patient will not affect the course of the eruption. Superficial x-ray, intradermal injections of hydrocortisone or prednisolone, solid carbon dioxide (Dry Ice) applied to the lesions, scalpel incisions of the papules, and punch biopsy of a papule have produced involution of the eruption. Spontaneous remission can also occur. Disseminated granuloma annulare has been treated successfully with intramuscular injections of either streptomycin[1] or bismuth.[2]

Submitted for publication Aug. 25, 1958.

Assistant Professor, Dermatology, New York Medical College-Metropolitan Hospital Medical Center (Joseph L. Morse, M.D., Director).

Report of Case

A white man, aged 26, first noticed the appearance of skin lesions on his buttocks in April, 1956. Within one month other lesions appeared on his feet, arms, abdomen, and back. The systemic and past histories were negative.

On physical examination on April 10, 1957, there was a generalized symmetrical eruption, which involved the buttocks, shoulders, lateral aspects of the lower extremities, the abdomen, and the volar

Fig. 1.—Plaque lesion.

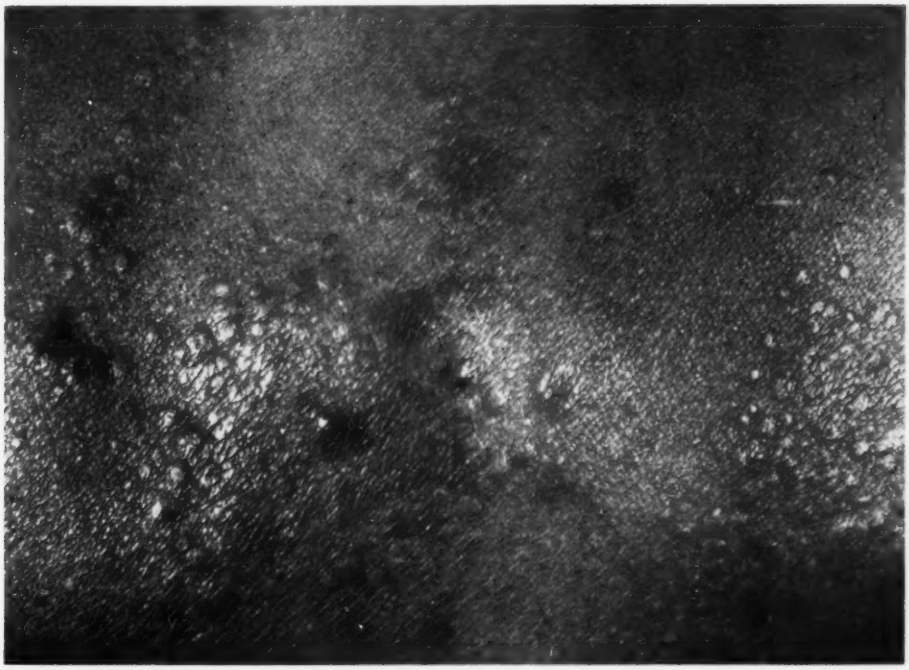

Fig. 2.—Papular lesion.

aspects of the forearms. Two types of lesions were present. Some lesions (Fig. 1) were hyperpigmented, oval, solid plaques which were distributed on the thighs and on the feet, whereas others (Fig. 2) were discrete skin-colored papules of 1 to 2 mm. in diameter. The latter type were present in large number (hundreds) over the back, chest, abdomen, buttocks, and upper extremities.

Biopsy (Read by Drs. Wilbert and Perry Sachs). "The complete picture shows the presence of granular changes within the collagen. About these there is a reaction containing epitheloid cells. The epidermis shows no significant changes."

Microscopic Diagnosis.—"Granuloma annulare."

Therapy.—Isoniazid, 300 mg. daily, with 50 mg. of pyridoxine for one month. Calciferol (Vitamin D_3), 100,000 units daily, for one month. Grenz-ray, 0.028 mm. of aluminum, half-value layer, 200 r, administered weekly. Maximum total dose received in any area, 800 r. The upper extremities, abdomen, and back were treated with this modality. Prednisone (Meticorten), 10 to 20 mg. daily, for three months. Injections of prednisolone (Meticortelone), 12 mg. per injection, once a week for four weeks, were made into the skin overlying the right scapula and the skin of the volar aspect of the left wrist. The lesions flattened, and many disappeared. Several sites became depigmented after the lesions had involuted. This treatment was impractical for the management of the entire eruption.

On Nov. 4, 1957, chloroquine phosphate tablets, 250 mg., one twice a day, were started. By Dec. 9, 1957, the lesions had almost disappeared. On Jan. 6, 1958, the skin eruption was no longer present. The chloroquine phosphate was stopped. On March 15, 1958, the patient noticed the appearance of lesions on his buttocks and upper extremities. Chloroquine phosphate tablets, 250 mg., one twice a day, were taken again, and within one month the lesions disappeared.

Comment and Summary

A case of disseminated granuloma annulare, resistant to various forms of therapy but responsive to chloroquine phosphate (Aralen) is presented. In view of the second response to treatment it is unlikely that the result is attributable to spontaneous remission.

532 Park Ave. (21).

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Spring Supports for the Drive Shaft of Planing Machines

MURRAY C. ZIMMERMAN, M.D., Whittier, Calif.

The weight and drag of the flexible drive shaft on standard model planers, as well as vibration and "bucking" if the shaft is bent at much of an angle, have annoyed users of this equipment. These drawbacks were previously overcome only by having an assistant hold up the flexible shaft to keep it relatively straight and weightless, immobilizing a nurse for as long as the planer was in use. Some new model planers incorporate a spring support holding up the shaft. A similar flexible spring support with 18-in. total projection is made to clamp on ironing boards to hold up the cord of a standard home electric hand iron. Thirty seconds' work with a pliers bends the end of one of these cord holders into a rough (about 1 in. diameter) circle to hold and guide the larger diameter flexible drive shaft of the planer. This is satisfactory, clamped on the stand of the planer * and/or on the operating table † near the patient's head (see illustration).

Three different brands of hand iron-cord holders, all slightly different but all satisfactory for this purpose, were shown to me by the first three small-town hardware stores I tried. They ranged in price between $1.00 and $2.00 and are apparently generally obtainable. They might also be ordered from the manufacturer or for $1.50, C. O. D., from the Don Cameron Company, Medical Supplies Division, 1054 Broxton Ave., Los Angeles 24.

301 E. Hadley Ave.

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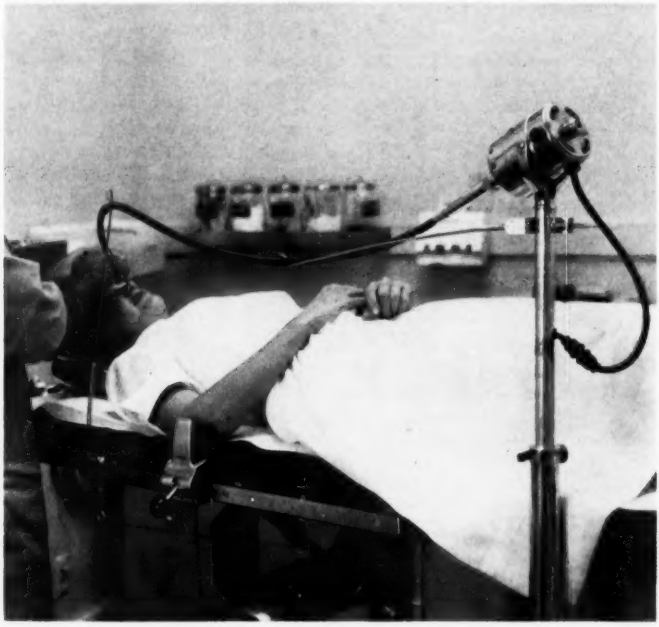
From the University of Southern California School of Medicine, Department of Medicine (Dermatology).

* Evertite Iron Cord Holder, Rich Household Products, Franklin Park, Ill.

† Kordtender, Jacob Auslander, Philadelphia 42.



Spring support for the drive shaft of planing machine.

Air Conditioning

A Modern Method for the Transmission of Parasites

ELMER R. GROSS, M.D., Wilmington, Del.

The realization that progress begets diagnostic problems confronted me this spring and summer when, during visits with family friends, I had occasion to treat their 7-year-old daughter for a textbook case of multiple bites. The clinical picture was clear. She complained of itching at night and of being unable to sleep; a morning examination revealed multiple urticarial papules with punctate centers, characterized by evanescent lesions.

Submitted for publication Sept. 3, 1958.

A cursory search of the child's room at first was negative, but after a careful examination the mother noticed on the bed particles of dust which appeared to move. Under the microscope these "dust particles" proved to be bird lice, which had been sucked in through the duct of the room air conditioner from a bird's nest outside the window. Removal of the nest cleared the child's condition.

Medical Arts Bldg. (1).

Society Transactions

THE CLEVELAND DERMATOLOGICAL SOCIETY

George M. Stroud, M.D., President
John A. Kenney Jr., M.D., Secretary
Robert Gardner, M.D., Reporter

Feb. 27, 1958

In Honor of Earl W. Netherton, M.D., Cleveland Clinic

Granuloma Faciale (Eosinophilic). Presented by Dr. G. H. Curtis and Dr. D. J. Grant.

A 39-year-old white man, employed as a typewriter repairman, was admitted to the Cleveland Clinic Hospital on Jan. 28, 1958. He complained of a lesion on the left cheek. It began as a small red pruritic spot just anterior to the ear and has been slowly enlarging. Alcoholic beverages seemed to produce swelling and increased erythema, but he has not observed any effect from sunlight. Previous therapy had consisted of solid carbon dioxide, liquid nitrogen, and local injections of steroids. This treatment did not appear to be beneficial, as the lesion continued to enlarge.

On the left cheek, anterior to the left ear and extending into the hairline of the temple, there is a sharply demarcated, dully erythematous, infiltrated plaque. The surface has a mottled appearance due to irregular-shaped areas of depigmentation with slight atrophy. In the center is an almost dead-white area of atrophy and sclerosis. The follicles in the lesion are somewhat patulous. The system review was noncontributory. Physical examination was not performed.

The Wassermann and Kahn reactions were negative. Laboratory data, including hemogram, urinalysis, blood sugar level, and blood cholesterol, were all within normal limits. X-ray examination of the skull, chest, and lungs was reported as normal.

The histologic examination showed the epithelium to be intact and essentially normal. The corium contained a dense but patchy infiltrate, separated from the epithelium by a narrow clear zone. The infiltrate was pleomorphic and contained eosinophils, polymorphonuclear leukocytes, lymphocytes, and an occasional plasma cell. Impression: granuloma faciale (eosinophilic).

Discussion

Dr. John A. Gammel: I agree with the diagnosis of granuloma faciale. Unusual are the scattered areas of atrophy and sclerosis. In the not too distant past, similar lesions would have been diagnosed clinically as lupus erythematosus, sarcoid, or lymphocytoma. The histologic picture is very typical. The epithelium is intact and a clear zone separates it from the infiltrate in the corium, consisting of polymorphonuclear leukocytes and eosinophils along with some plasma cells. The changes in and around the blood vessels are not as marked as in some cases reported. Pinkus (*Arch. Dermat. & Syph.* 61:442-454 [March] 1950) suggested the term granuloma faciale with eosinophils to differentiate it from the reticuloeosinophil granulomas of skin and bone.

A great deal of work has been done on eosinophilic granulomas since the end of World War II. When Weidman, in 1946, presented the subject in his presidential address before the American Dermatological Association (*Arch. Dermat. & Syph.* 55:155-175 [Feb.] 1947), he classified the eosinophilic granulomas into idiopathic (leukotic) and symptomatic groups and enumerated 13 different types. He pointed out that we are not dealing with an entity but only a histologic syndrome. He suggested that we speak of "eosinophilic granulomas" and not of "eosinophilic granuloma" as of one. Observations in the last 13 years have brought to light a multitude of facts but not a common denominator. "Lipoid granulomatosis" covers a large group but is not all-inclusive. The pseudoeosinophilic granulomas of the skin of various parts of the body and mucous membranes—a term coined by Pinkus—have been observed in connection with Hodgkin's disease, mycosis fungoides, deep mycoses, lymphosarcoma, Loeffler's syndrome, orificial tuberculosis, erythema elevatum diutinum, and other basic diseases, such as diabetes insipidus. Insect bites, too, may leave pseudoeosinophilic infiltrates. Eosinophilia in the blood is rarely marked and often absent.

The eosinophilic granuloma of the face should be separated from others. It attacks the healthy person, is limited to the face, and is not part of an internal disease. It is characterized by its chronicity and resistance to treatment, including radiation, except perhaps contact x-ray. The in-

filtrate is not lymphomatous but inflammatory. The numerous polymorphonuclear leukocytes are quite in contrast to its slow torpid course. The eosinophils may be greatly increased in the early stages and missing entirely in old lesions.

The eosinophil granuloma of the bone, first observed by Finzi, in 1929, usually clears up within the course of a year. There are now about 10 cases on record where eosinophilic granuloma of the skin and bone were present simultaneously. In all patients except one there were multiple lesions in both skeletal and integumental systems.

Reticuloeosinophilic granulomas are seen in patients with Abt-Letterer-Siwe disease and the reticuloendotheliosis of Hand-Schueller-Christian. Eosinophilic granulomas in children in the course of systemic diseases are rare and usually fatal. The eosinophilic granuloma of the bone goes through four stages and may show xanthomatous changes. Dr. Netherton, in 1944 ,reported the case of a woman with lupus erythematosis with superimposed xanthomatous infiltration. I wonder if he has gone over his slides again after Lever (*Arch. Dermat. & Syph.* 55:200 [Feb.] 1947) raised the question whether his case was not eosinophilic granuloma.

Lausecker (*Ztschr. Haut. u. Geschlchtkrank. 22*: 329-334 [June] 1957) has recently given a good critical review on the status of these granulomas. The suggestion of Pinkus to divide them into reticuloeosinophilic and pseudoeosinophilic granulomas will probably stand until further observations bring out more information as to etiology or basic disease. Up to now we feel justified to consider the eosinophilic granuloma of the face as an entity separate from others.

DR. JEROME Z. LITT: I should like to suggest a short course of therapy with chloraquine or Atabrine.

DR. EARL W. NETHERTON: Thank you, Dr. Gammel. In answer to your question about the case I reported, at the time we were studying that case I submitted a number of histological sections to Dr. Weidman. I had a communication from him later, and he asked me to go over the facts again; he did not recall whether or not there were any eosinophils. I got them out, and there were none. The histological picture was not like this particular case. It is interesting that you should mention it, because Dr. Weidman asked me to check on the same point you brought up.

Dermatofibrosarcoma Protuberans. Presented by DR. J. R. HASERICK and DR. G. R. CAMPBELL.

A man, aged 71, was first seen in the Cleveland Clinic in July, 1957, with the complaint of urinary incontinence. He also stated that 10 or 12 years ago he had had a "growth" removed from the left scapular region. This healed, leaving a depressed scar. Since April, 1957, a protruding mass had been growing in that area. Family history was noncontributory. There is vague information that the patient had an injury to the left scapular area years before the appearance of the first mass.

Examination reveals a polypoid tumor 2 to 3 cm. in diameter on the left suprascapular area. It is firm and purplish-red in color and overlies the 6×8 cm. indurated base. It appears to be superficially located. The prostate gland reveals a Grade IV enlargement. It is smooth, with no nodules apparent. The rest of the physical examination is negative.

The blood cell count on admission showed the hemoglobin to be 12.6 gm.; leukocyte count, 7,050; cell volume, 40 cc. The urinalysis revealed the pH to be 7.0; specific gravity, 1.015; albumin, 3+, with no sugar but many erythrocytes. The blood urea was 49 mg. per 100 ml.; serum phosphorus, 3.8 mg.; acid phosphatase, 1.4 Bodansky units. A roentgenogram of the lungs revealed pulmonary metastases; adenomatosis and alveolar-cell carcinoma could not be excluded. There were fluid and an air cyst present in the lung. A roentgenogram of the left shoulder revealed normal bony structure.

Histologic study reveals a fibroblastic and perhaps angiomatous tumor containing lipophages. Histologically this fragment resembles dermatofibroma, but it is of greater depth than usual. Other angiomatous tumors and fibroblastic neoplasms would have to be excluded by further biopsy.

The lesion was treated with 2,400 r x-ray, given in 300 r doses, with no apparent regression.

Discussion

DR. EARL W. NETHERTON: This patient was not here, but we would like to have the discussion anyway.

DR. GEORGE W. BINKLEY: I was happy to see this demonstration. There need be no apologies for the absence of the patient, because the excellent photographs and the protocol present all the data.

It has been twenty years since I studied this entity. To my knowledge, nothing new has been added. The lesions appear and develop slowly. The original report on this disease was by Darier and Ferrand, in 1924. After presenting four cases, they stated, "The lesions appear to have a predilection to pronounced siege, otherwise exclusive, for the skin of the anterior region of the abdomen and the neighboring inguinal regions." (Darier and Ferrand: Dermatofibromes, progressifs et recidivants, *Ann. dermat. et syph.* 5:545-562 [Oct.] 1924.) My study showed that dermatofibrosarcoma is found to the right or the left of the midline, extending down the back, with an exceptional report of a case of one each on a foot, the buttocks, and the penis. At this time, I believe these latter

cases are probably variants of sarcoma and that true dermatofibrosarcoma does have a strong tendency to localize at or near the mammary ridge. The case presented is on the extended mammary ridge. The prognosis in early dermatofibrosarcoma is good. If you have a good liaison with the surgeon, insist on wide and deep excision.

Arthur Hertzler, as early as 1926, pointed out that this tumor, when inadequately handled by insufficient excision, would recur once or twice and, after 20 to 40 years, become much more extensive and metastasize. (Hertzler, A. E.: Fibrosarcoma Tumors of the Skin of the Trunk, Characterized by Attenuated Dermal Surfaces. *Ann. Surg.* 84: 489-496 [Oct.] 1926.) This fact was reiterated by Mopper, in 1953. The histological findings of this case struck me as being more aggressive than early dermatofibrosarcoma. In the cases I studied, the lesions were well circumscribed on the borders. Also, there were lacunae, which indicated a slowly growing tumor. This case shows more invasiveness into the surrounding connective tissue. When we correlate these findings with the chest radiograph, we suspect that this is one of the more aggressive dermatofibrosarcomas.

DR. JOHN R. HASERICK: Do you think the pulmonary lesions are metastases of the dermatofibrosarcoma protuberans?

DR. GEORGE W. BINKLEY: I do not know. I do not recall seeing lung radiographs in the previous reports.

DR. GEORGE H. CURTIS: About four months ago I had the opportunity of seeing a Negro woman who had a dermatofibrosarcoma protuberans of the right lower quadrant, close to the inguinal region.

DR. JOHN R. HASERICK: The protocol of this case was presented to the Histopathologic Round Table at the Academy of Dermatology, in December, 1957. There is no doubt that he has dermatofibrosarcoma protuberans, and there is no doubt that he has pulmonary metastases. The question then, as now, is whether there is a relationship between the two conditions. The histologic picture of dermatofibrosarcoma protuberans is so benign that it is almost inconceivable that it could produce pulmonary metastases; yet Mopper and Binkley have both pointed out this possibility in the past. A biopsy of the lung would settle the question, of course, but his physical condition has been too poor to permit this study.

Dermatomyositis: Presented by DR. J. R. HASERICK and DR. D. J. GRANT.

A 10-year-old white boy was admitted to the Cleveland Clinic on Nov. 25, 1957, complaining of weakness, generalized muscle ache, difficulty in swallowing, and a rash on elbows, knees, face, and ankles. The patient was in good health until Oct. 3, 1957, when he developed an influenza-like illness with fever and general malaise. After four days of bed rest, the fever subsided and he returned to school. One week later he suddenly developed myalgia, first in his legs, then generalized. This was rapidly followed by marked weakness, most pronounced in the morning. In two days a rash appeared on the arms, elbows, and knees. After initial ambulatory treatment he was hospitalized elsewhere. A muscle biopsy revealed chronic nonspecific interstitial myositis. After discharge, weakness persisted without, however, febrile episodes. The family history was noncontributory.

The patient presented a pale and pasty appearance, with a faintly erythematous, maculopapular, eruption situated on slightly dark and thickened skin on the knees, face, knuckles, elbows, and ankles. Physical examination disclosed a thin, small, well-developed boy with marked weakness but in no acute distress. His weight was 67 lb.; temperature, 98.2 F; blood pressure, 105/70. There was cyanosis of the finger tips. The right elbow was limited to 40 degrees of extension; his grip was very weak, and he demonstrated a slightly spastic walk, with an obvious attempt not to bear weight on his right heel. The reflexes were normal.

The urinalysis was normal. The hemoglobin was 13 gm.; cell volume, 40 cc.; leukocyte count, 6,650, with 47% neutrophiles, 4% eosinophils, 45% lymphocytes, and 2% monocytes. The sedimentation rate was normal. A fasting blood sugar was within normal limits. Wassermann and Kahn reactions were negative. The L. E. test was negative. A 12-hour urine creatine was 272.1 mg., and the creatinine was 475.2 mg. X-ray of the chest was normal. An EMG was abnormal, with low voltages and fibrillation potentials.

Histologic examination showed no evidence of fibrinoid degeneration. There was some slight invasion of the muscle tissue by polymorphonuclear leukocytes, and numerous small round cells were seen in the interstitial spaces, between muscle fibers. The muscle fibers are of normal size and shape. Cross striations are normal. Impression: chronic interstitial myositis, nonspecific.

Therapy with Calcium Versenate was started on admission to the Cleveland Clinic Hospital. We administered 3 gm. in 1,000 cc. of dextrose solution intravenously daily for sixteen days. At the end of this time, the patient was discharged, to continue the Calcium Versenate orally at home. This was administered orally, 1 gm. t. i. d. The child was last seen on Feb. 12, 1958, by which time he had returned to school and had regained his normal activity. The skin changes had disappeared, and the gastrocnemius tightness had been relieved, and so his gait had returned to normal. Calcium Versenate dosage was gradually reduced, so that by Feb. 12, 1958, the dose was 0.5 gm. daily.

Discussion

DR. HERBERT H. JOHNSON, JR.: I do not propose to discuss this case in any detail, but I should report that this patient was seen in consultation on one occasion in another hospital about three months ago. The classical lesions of dermatomyositis, with elbow and knuckle erythema and atrophy, so characteristic of the condition, as well as the muscle weakness and tenderness, were present at that time. Seeing him now, it would be hard to believe that those lesions were there. There was no question about the diagnosis in my mind at the time. I should like to hear more about the therapy.

DR. JOHN A. KENNEY, JR.: I should like to ask Dr. Haserick what his experience has been with cortisone in dermatomyositis.

DR. JOHN R. HASERICK: I do not know the rationality behind the use of the chelating agents in this group of diseases. It may have been another example of serendipity, in which case, if it works, some bright fellow will come along and tell us why. With respect to cortisone in dermatomyositis, we have been inclined to reserve it for the severest cases of this disease. We do not feel that we get nearly as dramatic a response as in systemic lupus erythematosus. We have in some cases maintained it for many months. I should say that we have had very few satisfactory results. We have had patients who are up and around, without taking any steroidal drugs, but unfortunately I can remember many who did very poorly. The Calcium Disodium Versenate is used when calcium depletion is not desired.

Psoriasis (Treated with Aristocort). Presented by DR. E. W. NETHERTON and DR. W. N. DAVIDSON.

A 56-year-old white man first came to the Cleveland Clinic in 1952, with a history of skin difficulty for 15 years. At this time he developed erythematous scaling plaques on the hands. Later the perianal region became involved. Previous treatment had consisted of numerous local medications and ultraviolet light, which were of no apparent benefit. His past history revealed a peptic ulcer in 1952.

On the initial examination, in 1952, there was involvement of the hands and perianal area. There were small- to half-dollar-sized, well-defined, dull-to-light-red raised plaques, with dry, mica-like imbricated scales. On other plaques, the surfaces were granular. A few of the fingernails showed some separation from the nailbeds. There was a well-demarcated, light-red plaque surrounding the anus.

Urinalysis, blood sugar level, and serology were normal. The blood cell count revealed 5,150 white cells, 12.5 gm. hemoglobin, and cell volume, 38 cc.

Histologic examination shows the stratum corneum to be wavy, forming many follicular dells. It is laminated and mostly parakeratotic. A few inflammatory cells are seen in the stratum corneum, but there are no clear-cut microabscesses noted. The epidermis is extremely acanthotic. The rete pegs penetrate deeply into the corium. The epidermal plates are thin and vary from four to six cell layers. A moderately heavy inflammatory reaction is noted in the papillae and to a lesser extent around the superficial vessels. The section is consistent with psoriasis but could also be a chronic localized neurodermatitis.

Tar preparations helped the patient for a time. He was also benefited by a salicylic acid-ammoniated mercury ointment. Chloroquine was given for several months, with equivocal results. Anthralin ointment was found to irritate. The lesions cleared during a course of 10 superficial x-ray treatments of 75 r but recurred when this was discontinued. The patient received a course of 11 injections of 1 cc. of colloidal manganese, without much improvement. On Jan. 14, 1958, he was given Aristocort, 4 mg. four times daily. Within two weeks there was a marked improvement. Since Feb. 11, 1958, he has been taking two tablets every second day.

Discussion

DR. CLYDE L. CUMMER: The reason for presenting this patient is that he responded so well to Aristocort. I think it would be rather trite for anybody to try to open the discussion on psoriasis, but there is one factor here which makes this a really live subject. The patient shown today had been a patient of mine for three years, from 1949 to 1952, and I tried practically everything on him, including painting the hands with tar, ultraviolet, and some x-ray. He did have a little improvement. The appearance of this man today is striking, and I think that it is marvelous that there is a drug of this kind that would do what has been done here. I realize that it is premature to ask these questions, but I would like to know what the presenters think of the length of time they can use this preparation and how long the beneficial results may last.

The problem of gastric ulcer with Aristocort comes up. I think it is very fortunate that it was not recognized that this man had a gastric ulcer and that the drug was started anyway, and apparently he has tolerated it very nicely.

DR. GEORGE W. BINKLEY: I think that Triamcinolone is an effective suppressant in psoriasis. According to J. L. Hollander's report, the percentage of response is high. He reports success in 13 out of 17 cases of chronic psoriasis. The side-effects are not serious. Of course, there is salt depletion, in contrast to older steroids. Instead of euphoria and accentuation of appetite, one may experience the opposite effects. We

should warn our patients that they may feel fatigue or slight depression in the beginning of the course of Triamcinolone. The use of the drug is palliative; there is no question about that. It is like any other steroid. When you stop the drug, the patient will be vulnerable to relapse. But I think it has something to offer chronic inveterate psoriasis, for we have nothing that equals it. I plan to use it similarly to what has been outlined for this patient, beginning with four tablets a day for a week, and then decrease stepwise. If I can maintain my patient on 8 mg. per day or, as in this case, on 8 mg. every second day, I do not anticipate serious side-effects.

DR. A. L. LEIBY: I have used Aristocort on three cases of generalized psoriasis, and I was surprised by the rapid response. These patients are on maintenance doses of 2 to 4 mg. of Aristocort daily. This maintenance dose has been the therapy for a one-month period following a beginning dose of 12 mg. daily.

DR. P. J. COSTELLO: I happen to be one of the more fortunate to have been trained under Dr. Netherton. I hate to come all the way from Philadelphia to put a damper on Aristocort. About a month ago, or perhaps a little later than that, there was an article in one of the Philadelphia papers, stating that one of the University of Pennsylvania groups, I think under Hollander, had done a great deal of work with Aristocort. This is a thing that has not been published as yet and probably will be. As mentioned before, when the drug is stopped, the psoriasis does come back. However, I think their experience has been very discouraging, in that it is very much more resistant to treatment than it was before when it does come back. I would still recommend the Goeckerman treatment.

DR. S. N. ULEVITCH: I have not used it in psoriasis but in a severe case of angioneurotic edema and hives. The patient was sensitive to the Aristocort itself and could not tolerate it more than two or three days. I used it in severe contact dermatitis of the hands, in which everything else had been used, and the patient developed a severe diarrhea from the Aristocort. I used it in a case of mycosis fungoides, and the response was miraculous; the man really improved on the drug in one week's time.

DR. GEORGE M. STROUD: I have had success in controlling several cases of psoriasis with Triamcinolone. Although I have not taken the opportunity to compare the effects of Triamcinolone and 6-methyl-prednisolone (Medrol), I noticed that in the January, 1958, issue of *Metabolism*, Diraimondo and Forsham mention that 6-methyl-prednisolone was 25% more anti-inflammatory, on the basis of its corticotropin-suppressing activity and results based on clinical usage.

DR. RUTH R. RAUSCHKOLB: I have had one patient, who has had much trouble, whom I have treated with Aristocort. We planned Goeckerman treatment for her, but patch-testing showed marked sensitivity to tar. She was frantic, and we put her on Medrol, at first with some improvement, and then on Aristocort. I have reversed her four times, and her response to the Aristocort is definitely superior.

DR. JOHN R. HASERICK: There is no question now about the powerful effect of Triamcinolone in the treatment of psoriasis. It is of interest that, despite its potency when administered systemically, it is ineffective in psoriasis when applied locally. At this time I would like to report on a patient who developed a large duodenal ulcer two and one-half weeks after Triamcinolone was started. This man has been under my care since 1953, and at no time has he ever had gastrointestinal manifestations. He was so grateful for the improvement in his pustular psoriasis of the palms that he continued to take the Triamcinolone without our knowledge, and despite our warnings.

Scleroderma, Localized. Presented by DR. J. R. HASERICK and DR. G. R. CAMPBELL.

Keratosis Follicularis. Therapeutic Suggestions? Presented by DR. J. R. HASERICK and DR. W. N. DAVIDSON.

Necrobiosis Lipoidica. Presented by DR. E. W. NETHERTON and DR. D. J. GRANT.

Urticaria Pigmentosa (Nodular Type). Presented by DR. J. R. HASERICK and DR. D. J. GRANT.

A Case for Diagnosis: (Scleroderma?) Presented by DR. K. H. BURDICK.

Acrosclerosis, with Severe Vasospasm. Presented by DR. GEORGE H. CURTIS and DR. W. N. DAVIDSON.

Cylindroma. Neurofibromatosis(?) Presented by DR. E. W. NETHERTON and DR. G. R. CAMPBELL.

Hypertensive Ischemic Ulcers of the Legs. Presented by DR. GEORGE H. CURTIS.

DETROIT DERMATOLOGICAL SOCIETY

Coleman Mopper, M.D., President
Alice E. Palmer, M.D., Secretary
Robert E. Burns, M.D., Recorder

March 12, 1958

Benign Hemosiderosis. Presented by DR. F. R. MENAGH.

DR. JAMES R. ROGIN: I should like to take this opportunity to point out that the diagnosis "benign hemosiderosis" is representative of one of the most confused groupings in dermatological nomenclature.

Let us examine the various entities in this group, as well as their formidable, confusing, and, in many instances, entirely meaningless names. First, there is Schamberg's disease, or "a peculiar progressive pigmentary dermatosis." Is it true that the disorder is really "peculiar" in that it can be differentiated completely from the other disorders in this group? I believe that it can not be so distinguished. The next word in the title, "progressive," is also meaningless, since all the other disorders in this group are also "progressive." The word "pigmentary" gives no clue that the pigment is of hemosiderin origin as contrasted to melanin or other types of pigment in the skin.

The second member of this group of diseases is Hutchinson's disease, or angioma serpiginosum. Actually, although this disorder is included in the "pigmented purpuric eruptions" the lesions are not purpuric but are, rather, punctate angiomatous lesions which, microscopically, show no diapedesis of the blood cells and no deposits of hemosiderin. The titles become progressively more formidable, since the third member of this group is known as Majocchi's disease, or purpura annularis telangiectodes or telangiectasia follicularis annulata. Clinically, the lesions may be telangiectatic, purpuric, atrophic, and, rarely, ulcerated.

The last member of this group is known as Gougerot-Blum disease, or pigmented purpuric lichenoid dermatitis or purpura angiosclereux prurigineux avec elements lichenoides! In this disorder, pruritus is usually very pronounced and the papules become lichenoid as a result of chronic scratching.

Microscopic examination does not clarify the issue in most cases. In all, the epidermis is normal and the significant changes occur in the cutis, where the capillaries are usually increased in size and in numbers and frequently changed in shape. The arterioles may be thickened and occasionally obliterated. Diapedesis of blood cells and hemosiderin deposits are common to all, with the exception of angioma serpiginosum, where these characteristics are absent, and perhaps for this reason angioma serpiginosum should not be included in this group.

To confuse the issue still further, I am sure that most of the members in this audience today have seen purpuric eruptions due to drugs or accompanying stasis of the legs that are indistinguishable clinically from these so-called "entities."

A stasis inadequacy seems common to all of these disorders and no demonstrable hematologic defects are found in any.

I should like to support completely the plea of Randall, Kierland, and Montgomery, who, in 1951, suggested that the entire group be lumped together as "pigmented purpuric eruptions." However, in Montgomery's most recent textbook there still exists the artificial and senseless separation of these disorders with their accompanying ridiculous nomenclature. My deepest sympathies are extended to the young men who are in training today and who must, I am afraid, still plan to hurdle these inane obstacles on their Board examinations!

Acne Conglobata with Septicemia (?). Presented by DR. ROBERT E. BURNS and DR. JAMES M. COLVILLE (by invitation).

A 16-year-old white male high school student had had mild acne of the chest and back for one year. During the football season of 1957, the chest and back lesions became more acute. The boy was an amateur taxidermist, and during the fall he worked with a deer carcass.

Treatment by his local dermatologist consisted of low-fat diet, sulfur lotion, and thyroid. After an increase in the acne lesions sulfisomidine (Elkosin, Ciba) was prescribed. The lesions continued to appear with increasing severity, and by January, 1958, they were frankly conglobate. He developed febrile reactions, with temperature as high as 103 F, and complained of joint and muscle pains.

He was admitted to his local hospital. There, repeated blood cultures and routine laboratory examinations were normal. Internists in consultation found no localizing noncutaneous signs. Chloramphenicol, novobiocin, tetracycline, sulfadiazine, and ristocetin were administered in full doses but without benefit. He was transferred to Henry Ford Hospital on Jan. 31, 1958.

On admission, numerous conglobate lesions of acne were found on the face, chest, and back. Those on the chest were particularly deep and confluent, with a gelatinous material filling each ulcerated lesion surmounting which was a thick en-

crustation. The slightest touch produced excruciating pain.

Laboratory examinations revealed Hb. 10.0 gm., W. B. C. 12,850. Differential count revealed polymorphonuclears 79%, eosinophils 3%, lymphocytes 16%, monocytes 4%. Platelets were of adequate numbers. Urinalysis showed an occasional granular cast but was otherwise normal. Serum electrophoretic studies showed a total protein 6.6 gm., with albumin 27% and globulins as follows: α_1 9%, α_2 21%, β 20%, γ 23%. Skeletal x-rays showed diffuse demineralization. Chest x-ray was normal. The following tests were normal: S. T. S., peripheral L. E. test, Coombs test, N. P. N., creatinine, A. S. O. titer. Agglutination tests for typhoid, paratyphoid A and B, brucellosis, and psittacosis were negative.

Skin tests to various fungi and to tubercle bacillus were negative. Aerobic skin cultures grew a few hemolytic, coagulase-positive Staphylococcus pyogenes var. aureus, sensitive only to erythromycin and neomycin. Anaerobic cultures produced a Gram-positive diphtheroid organism eventually isolated as probable Corynebacterium acnes. Repeated blood cultures were consistently negative. A biopsy specimen of an acne pustule contributed no new information. Cultures and special stains of this tissue were negative for bacteria and fungi.

Treatment consisted of supportive measures, including repeated transfusions. Local compresses of various types and antibiotic ointments were utilized. Aqueous penicillin, 1,000,000 units I. M. q. 2 h. and 4,000,000 I. V. b. i. d., was given from Feb. 15, 1958, to March 3, 1958, when it was discontinued because of the appearance of urticaria. The temperature leveled off and, following the completion of the treatment, remained low with swings to 99.6 F.

DR. ROBERT E. BURNS: Dr. J. M. Colville has a special interest in systemic bacterial infections and gave us great help in this problem.

DR. JAMES M. COLVILLE (by invitation): When we first saw this patient he was septic and appeared to be going down hill. We agreed that the skin itself could not account very well for the entire picture of this boy's illness. The degree of toxicity, the anemia, and the arthralgias all suggested a generalized disease, probably sepsis. We made some very aggressive attempts at isolating organisms from the blood, including several bone marrow cultures, as well as many venous blood cultures. Unfortunately, these studies were singularly unrewarding. We then turned our attention to the bacteriological flora of the skin lesions. This was done by isolating several of the new lesions and doing stab cultures of these lesions. Two organisms were isolated. One was a Gram-positive rod and the other was a Gram-positive coccus. The latter organism was identified as a coagulase-positive hemolytic S. pyogenes var. aureus. It was penicillin- and tetracycline-resistant, the type we usually associate with hospital infections occurring in persons who have received previous antimicrobial agents. The Gram-positive rod was identified as either Erysipelothrix or C. acnes and was sensitive to penicillin. In the literature one can find descriptions of Erysipelothrix causing skin lesions, arthralgias, and endocarditis. On the basis of the clinical picture and the failure to isolate staphylococci from the blood, we felt that there was at least a possibility that the Gram-positive rod was significant. We treated him with very large doses of penicillin, and there occurred a rather gradual fall in his temperature and visible, however far from complete, improvement of the skin lesions. We have not as of today isolated this organism from his blood. Penicillin was discontinued because the patient developed a sensitivity to the agent. He was placed on diphenhydramine (Benadryl), and now continues to run a low-grade fever. I am afraid we have not shed much light actually on the case, but I think he is improving. We have never been able to fix this as a staphylococcal sepsis. However, it could be one in spite of the fact we have not isolated this organism from the blood because they do occur in an intracellular position and may remain hidden for long periods of time.

DR. CLARENCE S. LIVINGOOD, Detroit: What are the other differential diagnosis possibilities?

DR. JAMES M. COLVILLE: I certainly think, as your group suggested, that a collagen disease has to be considered. I do not know whether this skin lesion is compatible with a collagen disease.

DR. CLARENCE S. LIVINGOOD: Well, no, but it is probably as compatible as it is with septicemia.

DR. ARTHUR C. CURTIS, Ann Arbor: How do you explain the arthralgia which came on with reduction in temperature and fall in white count?

DR. JAMES M. COLVILLE: Actually, this symptom is no longer present. It was present only when he was running a septic course. As a matter of fact, he is feeling very well now. We have never seen a hot joint on this boy.

DR. ROBERT E. BURNS: It is purely a philosophical approach, but one sometimes wonders if these severe skin lesions could be in the nature of a Schwartzman phenomenon associated with sepsis elsewhere.

DR. R. RICHARD HARRELL, Ann Arbor: A similar case, though perhaps not so severe a one, came under our care some months ago. He had severe ulcerations and some fever but no myalgias or arthralgias. Tremendous benefit was obtained by curetting the ulcerated lesions under general anesthesia. This was carried out on Dr. Curtis' advice.

[ADDENDUM: Dr. Harrell's suggestion was later acted upon with distinct benefit to the patient. His

general health improved, though pustular acne lesions continued to appear. Debrided ulcerative areas of the chest wall have healed slowly, and skin grafting is anticipated.]

Idiopathic Atrophoderma of Pasini and Pierini. Presented by Dr. C. S. Livingood.

Incontinentia Pigmenti. Presented by Dr. R. P. Fosnaugh (by invitation).

Diffuse "Collagen" Disease. Presented by Dr. C. S. Livingood.

Ulerythema Ophryogenes. Presented by Dr. C. S. Livingood.

Multiple Epitheliomata. Presented by Dr. R. E. Burns.

Lupus Erythematosus (?). Presented by Dr. F. R. Menagh and Dr. B. M. Hamil (by invitation).

Lichen Nitidus—Generalized. Presented by Dr. C. S. Livingood.

Subcorneal Pustular Dermatosis (Sneddon and Wilkinson). Presented by Dr. R. E. Burns.

Stasis Ulcer—A Therapeutic Approach. Presented by Dr. Joseph Beninson.

Melanoma of Face. Presented by Dr. Eugene A. Hand, Saginaw.

Rosacea with Rhinophyma. Presented by Dr. Eugene A. Hand, Saginaw.

Epidermolysis Bullosa. Presented by Dr. C. S. Livingood.

PHILADELPHIA DERMATOLOGICAL SOCIETY

James M. Flood, M.D., Chairman
Herbert A. Luscombe, M.D., Secretary

April 18, 1958

Hypertrophic Lichen Planus? Mycosis Fungoides? Presented by Dr. Carroll F. Burgoon and Dr. Joseph S. Harun (by invitation).

A Negro man, aged 48, presented generalized reticulated hypo- and hyperpigmented, large, plaque-like lesions with a grayish hue on the face and pretibial regions. The patient's previous lesions of the mouth and genital regions have now cleared. The patient was hospitalized at the Philadelphia General Hospital in November, 1956, with a generalized pruritic eruption, and from Jan. 30, 1957, to May 24, 1957. The diagnosis was hypertrophic lichen planus.

The patient has been treated at the Philadelphia General Hospital for five months with a generalized pruritic eruption which has since regressed, leaving residual lesions of the perioral, malar, and periorbital regions.

On admission a year ago, medical examination disclosed generalized lymphadenopathy; otherwise, the general physical examination was negative.

Blood revealed 12.4 gm. hemoglobin. The liver profile was normal. The albumin-globulin ratio was 4.7:2.6. The serologic tests for syphilis were nonreactive. The electrocardiogram was normal. Barium enema and examination of the upper gastrointestinal tract were negative. Blood calcium was 10.0 mg. %.

The report on the biopsy specimen from a lymph node was "dermatopathic lymphadenopathy." The reports of skin biopsies were as follows: On Feb. 4, 1957, exfoliative dermatitis; on Feb. 12, 1957, nonspecific dermatitis; on April 8, April 9, and April 22, 1957, lichen planus. The report on a biopsy specimen taken from the tongue on April 22, 1957, was lichen planus.

The patient was treated during May, 1957, with corticosteroids without improvement; with superficial roentgen ray to ankles, shoulders, and face from June to Aug., 1957, intermittently, with remission of the lesions.

Discussion

Dr. J. M. Schildkraut, Trenton, N. J.: That has all the earmarks of hypertrophic lichen planus, but it is rather unusual for it to run together into large plaques, especially on the face. I have never seen lesions so extensive. This might be going into mycosis fungoides, although I do not remember ever seeing a case of lichen planus that developed into mycosis fungoides.

Dr. Margaret Gray Wood: Histologically, this is mycosis fungoides. The sections which have been interpreted as lichen planus are entirely consistent with poikiloderma. This patient has mycosis fungoides with associated poikiloderma.

Dr. Albert M. Kligman: It seems to me that all the views can be composed, because mycosis fungoides is not a disease *sui generis* but a complication of a long-standing preexisting condition—lichen planus, parapsoriasis, and neurodermatitis. This man could very well have had lichen planus to begin with which has now finally degenerated into a neoplastic process.

Dr. Herman Beerman: Some years ago Dr. Thomas and I searched the literature for references to various premycotic diseases, and I cannot recall lichen planus among them, and so if this gets into the record, I request that Dr. Kligman supply us with documentation. I believe many of these patients receive erroneous diagnoses in the beginning; they are mycosis fungoides from the start, and we are unable, by our present means, to recognize them. Dr. Fanburg had a patient in this same category who had a dozen biopsies before one of the specimens showed mycosis fungoides.

DR. ALBERT M. KLIGMAN: I have no documentation, but if one looks through the literature and talks to men of experience one hears that persons who eventually develop mycosis fungoides have received various diagnoses, among which have been lichen planus and even psoriasis. Premycotic mycosis fungoides is not a definitive diagnosis. It is a disease of varying categories, some known and some unknown, which eventually degenerate.

DR. IRA L. SCHAMBERG: I agree with Dr. Kligman's concept of this condition. It is a fascinating thing that a variety of diseases—erythroderma, poikiloderma, parapsoriasis—may, after many years, eventuate in this malignant condition, which frequently at autopsy is diagnosed by the general pathologist as leukemia or lymphoma.

Facial Hemiatrophy? Scleroderma? Herniated Nucleus Pulposus L 4-5. Presented by CAPT. JAMES H. LOCKWOOD (MC), U. S. N.

A white man, aged 20, well developed and nourished, with no apparent illness, presented over the forehead, on the side of the nose, and on the temple on the left patchy areas of atrophy causing the skin to have a wrinkled appearance. The lesion did not extend above the hairline, and the eyebrow was not involved. There was associated total anesthesia. The patient had the usual childhood illnesses without complications or sequelae. In 1954, he sustained a low back injury while playing football, with pain over the lower back and the right leg in the distribution of the right sciatic nerve. He was treated with bed rest, with relief of the acute symptoms, but he has had occasional back and right leg pain since. In May or June, 1957, he had insidious onset of "numbness" over the left side of his forehead, followed by loss of sweating and gradually progressive wrinkling of the skin in same area during the ensuing two or three weeks. The "numbness" gradually progressed to total anesthesia over the distribution of the ophthalmic division of the left trigeminal nerve. Two to three months later he first noted recurring sharp, stabbing retro-orbital pain behind the left eye. About four months after the onset of his present illness, he had a febrile illness, with sore throat, rhinorrhea, and general malaise, diagnosed as "flu," for which he was treated with various antibiotics, including penicillin. At that time he was first noted to have a miotic pupil on the left. His visual acuity at that time was 20/30 O. S. Two to three weeks later he began having gradual diminution of his visual acuity in the left eye, and early in January, 1958, he awoke one morning to find that he was totally blind in the left eye, except for the ability to perceive light. There has been very little subjective change since January, 1958, except for gradual extension of the area of anesthesia, loss of sweating, and wrinkling of the skin on the left side of the nose and the left temple.

In addition to the above findings, there were corneal anesthesia, miosis, and amaurosis of the left eye. Over the lateral aspect of the right leg there was hypesthesia from the iliac crest down to and including the foot. This latter finding was interpreted as due to a herniated nucleus pulposus between L4 and L5 as a result of the football injury in 1954. The remainder of the physical examination was essentially within normal limits. Vestibular-function tests showed absent rotatory component to nystagmus on the left.

The following laboratory studies and x-ray studies were all within normal limits: Complete blood cell count; urinalysis, erythrocyte sedimentation rate; blood urea nitrogen; fasting blood sugar; total protein and albumin-globulin ratio; acid phosphatase; alkaline phosphates; VDRL; spinal fluid examination; roentgenograms of the chest, skull, and cervical and lumbar spine, and left carotid arteriogram. A pneumoencephalogram was unsatisfactory, owing to inadequate filling of the ventricles.

Reports on biopsy specimens were as follows:

Jan. 13, 1958, U. S. Naval Hospital, Camp Le Jeune: Skin of forehead showed atrophy of skin and fibrosis of dermis but was interpreted as insufficient for a diagnosis of scleroderma.

March 4, 1958, U. S. Naval Hospital, Philadelphia: Interpreted by Dr. Herman Beerman as possible scleroderma.

April 11, 1958, U. S. Naval Hospital, Philadelphia: Biopsy including both normal and abnormal skin of forehead diagnosed as scleroderma.

No treatment has been given at this time.

Discussion

LT. DONALD BAXTER (MC) U. S. N.: This entity was reviewed in the English literature by Archambault and Fromm, in 1932. At that time

there had been 400 cases of facial hemiatrophy reported; since then there have been about 23 reported. The entity seems to comprise a variety of clinical types, the etiology of which is not thoroughly understood. It seems to develop most frequently in the second decade. The disease may start at any point on the face and may progress to total facial hemiatrophy or even extend beyond the face or stop at any point. Osborne, in 1922, reviewed the literature for cases associated with morphea or morphea-like lesions. Of some 400 cases in the literature, only eight cases were found to coexist with morphea. We feel that our biopsies on this patient certainly suggest scleroderma. Dr. Beerman has reviewed the slides and might wish to comment on them. The most frequently recognized mechanism in facial hemiatrophy is a lesion of the sympathetic nervous system. Our patient certainly shows some evidence of sympathetic involvement. He has a miotic pupil and absence of sweating on the affected side, but he presents several things that are somewhat of a problem. The blindness of the left eye and total anesthesia of the ophthalmic division of the left trigeminal nerve now spreading in the maxillary division are difficult to explain on the basis of a lesion of the sympathetic nervous system.

DR. JOHN P. SCULLY, Reading, Pa.: Is there any reason to suspect that this man has a brain tumor?

LT. DONALD BAXTER (MC) U. S. N. (by invitation): He has been fairly thoroughly studied by the Neurological Service. There is no indication that there is a brain tumor. A pneumoencephalogram was attempted but was unsatisfactory due to unsatisfactory filling of the ventricles. There is no other evidence to suggest a brain tumor, and the peripheral lesions he has are of such a diverse nature that it would be difficult to pin them down to any single central nervous system lesion. Dr. Alpers says the lesion is peripheral rather than central.

DR. HERBERT M. LEAVITT, Easton, Pa.: The lesion is clearly in the peripheral portion of the fifth nerve; the seventh nerve seems to be skipped; the eighth is involved, and then, of course, there is the blindness and amaurosis of the left eye. What do they think of the possibility of some type of meningitic process, some fibrotic thickening, perhaps involving certain nerves and not others?

LT. DONALD BAXTER (MC) U. S. N. (by invitation): It would be difficult to explain the sympathetic involvement on the basis of a meningitic mechanism. Archambault and Fromm, in their review of the literature, found that there were many patients who did show anesthesia of the affected area. This has developed since he came on active duty.

DR. IRA L. SCHAMBERG: Has there ever been a reported case of blindness in facial hemiatrophy?

LT. DONALD BAXTER (MC) U. S. N. (by invitation): Barber listed several cases in his report in 1922 and Archambault, in 1932. Nothing was mentioned as to the pathogenesis.

DR. ALBERT M. KLIGMAN: Had he a herpes zoster? This facial lesion is not typical of hemiatrophy. It is a rather superficial lesion of the skin, and hemiatrophy is not particularly a neurological disorder.

CAPT. JAMES H. LOCKWOOD (MC) U. S. N.: I think it can be explained by the fact that we are seeing this in a very early stage. In the next few years we shall see more involvement. It is not extensive now, but I think we shall see other organs and other tissues involved as time goes on.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I did not see too much atrophy, and the patch on the forehead seemed to have a dead-white appearance and comedone lesions resembling lichen sclerosus et atrophicus.

DR. LOUIS JAFFE: Did this man have any café au lait spots?

1. Neurofibromatosis—Cutis Laxa Left Lower Extremity. 2. Congenital Heart Disease—Pulmonary Stenosis. Presented by DR. CARROLL F. BURGOON and (by invitation) DR. JOSEPH S. HARUN.

A white man, aged 25, presented multiple flat to pedunculated fleshy lesions, present more prominently on the anterior and posterior trunk, associated with café au lait spots. The left lower extremity was markedly enlarged up to and including the gluteal region. The patient has congenital heart disease and pulmonary stenosis. He has had swelling of the left leg since childhood. He has been admitted to the Philadelphia General Hospital three times and states that he has had cutaneous lesions and swelling of his left leg as far back as he can remember. In November, 1957, his left leg began to drain, which prompted his first admission. This third time he has been admitted for surgery to his left leg.

Medical examination revealed a harsh Grade 4 pulmonary systolic murmur with a palpable thrill.

Blood showed 11.1 gm. hemoglobin. The blood sugar was 94 mg. % and blood urea nitrogen 10 mg. %. The urinalysis was within normal limits. The electrocardiogram showed a right axis deviation and right ventricular hypertrophy. Roentgenogram of a tumor mass in the left leg showed a possible plexiform neuroma.

The report on the biopsy of mass removed from the left lower extremity on March 5, 1958, was neurofibroma.

The patient has been treated with tetracycline, 250 mg. four times a day, and 600,000 units of penicillin q. 12 h.

Discussion

DR. THOMAS BUTTERWORTH, Reading, Pa.: The proper name for this is elephantiasis neuromatosa, but I agree with the presenter's diagnosis. The leg is beginning to smell bad, but if you try to cut it off, you may have a death on the operating table, and if you miss that, you may stir up a neurofibrosarcoma. I do not know what to do.

DR. JOHN E. GERMAN, Reading Pa.: That boy also has cutis hyperelastica with a subcutaneous nodule on the underside of his right forearm, and the joints of his fingers are very flexible. It is very common to see multiple dermatological anomalies, and the discovery of one alone should not preclude full examination of the patient.

Mycosis Fungoides: Tumor Stage. Presented by DR. CARROLL F. BURGOON and (by invitation) DR. J. S. HARUN and DR. R. RESTIFO.

A Case for Diagnosis: Pulmonary Emphysema. Dupuytren's Contracture, Bilaterally; Left Hemiparesis; Seborrheic Keratoses; Secondary Syphilis. Presented by DR. IRA L. SCHAMBERG.

Sarcoidosis. Presented by DR. CARROLL F. BURGOON, DR. J. S. HARUN (by invitation), and DR. R. RESTIFO.

Dermatitis Herpetiformis. Presented by DR. CARROLL F. BURGOON, DR. J. S. HARUN (by invitation), and DR. R. RESTIFO.

Superficial Epitheliomatosis: Purpura—Etiology? Benign Prostatic Hypertrophy; Chronic Brain Syndrome. Presented by DR. CARROLL F. BURGOON and DR. J. S. HARUN (by invitation).

Congenital Keratoderma: Palms and Soles. Presented by CAPT. J. H. LOCKWOOD (MC) U. S. N.

Secondary Syphilis; Tinea Versicolor; Condyloma Lata. Presented by DR. CARROLL F. BURGOON, DR. J. S. HARUN (by invitation), and DR. R. RESTIFO.

Linear Naevus; Vesicular. Presented by DR. MARGARET GERLACH MAHONEY.

Lupus Erythematosus: Chronic Discoid Type. Presented by DR. CARROLL F. BURGOON, DR. J. S. HARUN (by invitation), and DR. R. RESTIFO.

Nodular Vasculitis: Probable Collagen Disease; Question of Relationship to Actual Lupus Erythematosus or Variant Between Rheumatic Fever-Polyarteritis. Presented by DR. JOHN P. SCULLY, Reading, Pa.

Pityriasis Lichenoides Chronica of Juliusberg: Interim Report—Clearing Progressively Until Four Days Ago. Presented by DR. JOHN P. SCULLY, Reading, Pa.

Pityriasis Lichenoides et Varioliformis Acuta: Intercurrent Episodes of Pityriasis Rosea and Varicella. Presented by DR. LOUIS HAFFE, Pottstown, Pa. and DR. ARTHUR F. MANN (by invitation).

SAN FRANCISCO DERMATOLOGICAL SOCIETY

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Feb. 21, 1958

Necrobiosis Lipoidica Diabeticorum with Alopecia Showing Sarcoid-like Reaction. Presented by COL. RAYMOND M. WILLIAMS (MC), U. S. Army.

A 35-year-old pregnant woman developed lesions over the anterior surfaces of both legs two years ago. Multiple lesions appeared within three months. In March, 1957, a small bald spot was found in the scalp, which rapidly enlarged to its present size of 4×8 cm. In July, 1957, in the left parietal region a second area of alopecia started, which is now 3×4 cm.

There are numerous discrete and confluent, slightly depressed, oval-shaped plaques over both shins (Fig. 1). These have a smooth surface and a translucent, slightly yellowish appearance. In the scalp are two large areas of alopecia, one in the superior occipital and one in the left parietal region (Fig. 2). The scalp in these lesions is thin, atrophic, yellowish red, smooth, and covered with telangiectatic vessels.

Of two glucose-tolerance curves, one was flat and one showed a slightly lowered renal threshold, as occasionally found in pregnancy. A two-hour postprandial blood-glucose level was 117 mg. %.

Fig. 1 (Case 1).—Necrobiosis diabeticorum, legs (U. S. Army photograph).

Fig. 2.—U. S. Army photograph.

The total serum protein was 5.5 gm.; albumin, 2.2 gm.; globulin, 3.3 gm., with a ratio of 1:1.5. The first strength PPD was questionable; second strength, strongly positive. A chest film is negative. Tissue from one of the leg lesions is compatible with necrobiosis, whereas that from the scalp shows a sarcoid-like reaction, with asteroid bodies (Figs. 3 and 4).

Discussion

DR. EDWARD J. RINGROSE: I feel that cigarette smoking plays an important part in the development of necrobiosis. This disease is associated with arteriosclerosis, and smoking by increasing ischemia may enhance the development of the lesions. Perhaps this occurs in other skin disorders in which there is vascular involvement, including xanthomatosis and perhaps lupus erythematosus. The relationship of these diseases to smoking should be further studied.

The patient presented has necrobiosis on the legs, but I think it is granulomatosis disciformis chronica et progressiva on the scalp. The one glucose-tolerance curve suggests a "prediabetic" state, and she may develop diabetes mellitus later.

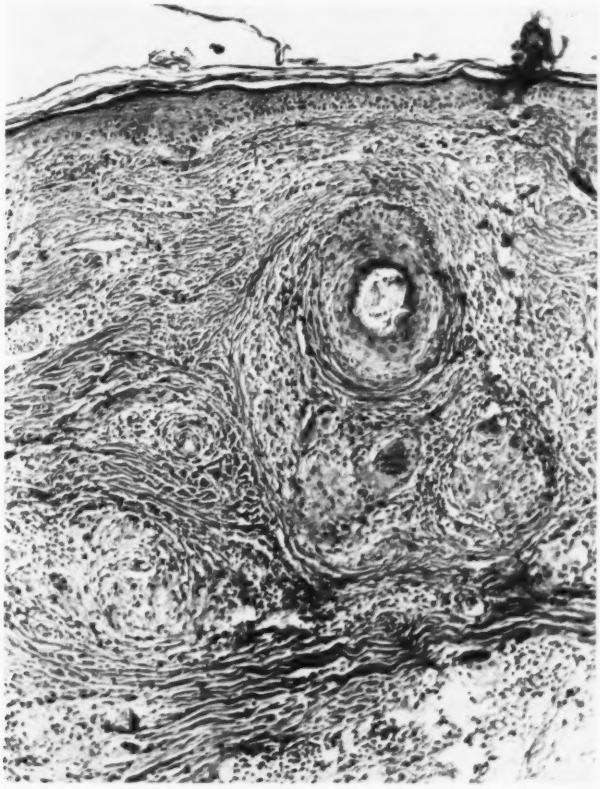


Fig. 3.—Sarcoid-like reaction, scalp; ×200 (U. S. Army photograph).

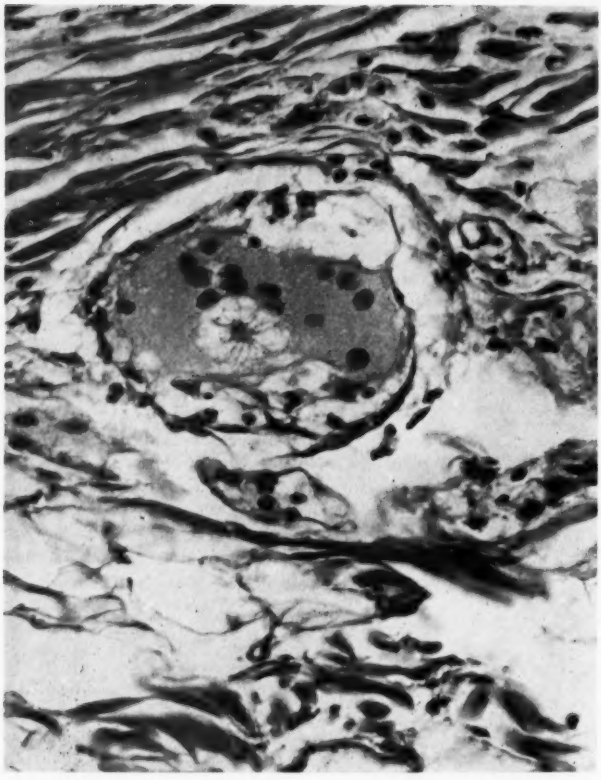


Fig. 4.—Asteroid body in giant cell, scalp; ×450 (U. S. Army photograph).

Asteroid bodies have been found principally in sarcoid but have been reported also in necrobiosis lipoidica diabeticorum.

DR. J. PETER MARK: I had occasion to see a patient with lesions on the legs and body which clinically and microscopically were necrobiosis, but there were many large foamy histiocytes and multinucleated giant cells. A skull film showed characteristic cannon-ball defects of Hand-Schüller-Christian's disease. Another patient with this disease had scarring alopecia. I suggest skull films be made on this patient.

DR. EUGENE FARBER: Since none of us know the etiology of necrobiosis we must depend on theories, and Dr. Ringrose's concept is a good one. The idea is that this is a near-infarct, equivalent to the ischemic ulcers of thromboangiitis obliterans or diabetic gangrene. Smoking may well be an aggravating factor in necrobiosis, as in Buerger's disease, but I doubt its role in lupus.

COL. RAYMOND M. WILLIAMS (MC) U. S. Army: Does this patient have sarcoidosis on the scalp and necrobiosis on the legs, or is this all the same process? It is my opinion that they are the same. There is certainly a different histopathological reaction in the two areas.

A Case for Diagnosis: Lupus Erythematosus?

Presented by CAPT. VICTOR J. SLOMINSKI (MC), A. U. S., and DR. MASAKO MIURA (by invitation).

A 24-year-old Puerto Rican man first noted a "pimple" on the left cheek, in 1953. He squeezed it and the area healed, with a depressed scar. A biopsy was performed on a nodule in the lower border, in 1954. In October, 1957, he noticed a pruritic moth-eaten type occipital alopecia. Two months later he erupted with subcutaneous hard white papules on the trunk and upper extremities, which have remained partially intermittent. The lesions are more noticeable when the patient is warm, as after a hot shower, and tend to fade when he is cool. At present they are regressing on the upper arms. Larger nodular lesions in arciform configuration around the elbows have flattened in the last week. During the past three to four weeks there have been swelling and pain in the finger joints and pain in the knees, elbows, and ankles. There is paronychial erythema at the base of each fingernail.

A positive serologic test for syphilis was found in January, 1952, and he received eight injections

of penicillin. There was no history of a primary lesion. On induction, in May, 1953, the spinal fluid was normal, but he was given 4,800,000 units of penicillin then, plus ten injections, in 1955, after a tonsillectomy. Because of a positive serologic reaction in March, 1956, a diagnosis of latent syphilis was made, and he was given another 9,000,000 units of penicillin. The spinal fluid was again normal in 1956, and the VDRL blood test, positive in four dilutions. He was given another 4,800,000 units of penicillin in August, 1957, for otitis media.

The pertinent results from extensive laboratory studies are summarized: Sedimentation rate, up to 13 mm. in one hour; VDRL, positive to four dilutions; total protein, 6.9 gm., albumin, 3.7 gm., globulin, 3.2 gm., ratio, 1.1:1; second strength tuberculin (PPD), strongly positive; two L. E. preparations, negative. A slide from the biopsy specimen from the right elbow contains basophilic collagenous degeneration, around which is a minimal round-cell infiltrate which also surrounds some of the appendages. There is a large vessel partially occluded by homogeneous eosinophilic material.

The patient has been taking 0.5 gm. of chloroquine daily since Jan. 31, 1958.

Discussion

DR. MORTIMER S. FALK: The generalized pruritic eruption began shortly after his most recent course of penicillin. This suggests an allergic penicillin reaction.

DR. PAUL FASAL: There was no microscopic evidence for lupus erythematosus, but it impressed me as the picture of urticaria. We do not often biopsy urticaria, but when it is done, this is exactly the microscopic pattern.

DR. HERBERT L. JOSEPH: While he may have a persistent urticarial reaction from penicillin, he could also have systemic lupus erythematosus. We know that patients with systemic lupus frequently have false positive serologic tests for syphilis, and I am not convinced that this man has or has had syphilis. I suggest a Treponema pallidum immobilization (TPI) or similar test with use of treponemal antigen. It might also be of value to obtain an isoelectric pattern on the serum and determine if the γ-globulin fraction is altered.

DR. WILLIAM EPSTEIN: I think this is a case of systemic lupus erythematosus. Gold reported upon this very subject (*Brit. J. Dermat.* 66:429, 1954), and similar cases have been seen by other dermatologists in France and England. I had the opportunity to see one of these cases with small nodules over the trunk. It is an unusual toxic reaction, and the nodules, which are transient, do not have the histopathologic picture of lupus but show collagen changes. We are fortunate to observe one of these rare cases.

DR. WILLARD M. MEININGER: Since the evanescent course and clinical appearance after administration of penicillin suggest a penicillin reaction, why not give him a trial with penicillinase?

ADDENDUM: Two positive L. E. tests have been found, and the TPI has since been reported as nonreactive.

Lepromatous Hansen's Disease. Presented by MAJOR EARL CLAIBORNE (MC), U. S. A. F.

This 21-year-old Hawaiian airman first discovered that he had Hansen's disease in 1949. His mother, who is 38 years old, has been in a leprosarium in Hawaii since 1942.

The patient was treated with sulfones in the same leprosarium for three years, after which he was discharged with continuation of treatment. One year later, he neglected to contact his physician for additional medication and lapsed treatment. When he entered the Air Force, he was relatively clear. Five months ago he noticed a red, elevated area on the right buttock and later swelling of the right face in which the sense of touch was lost. Pea-sized nodules appeared on the legs and left forearm one month ago, with loss of hair on the lower legs. His left hand has become numb, and he has burned himself several times without realizing it.

There are extensive macular lesions of the right cheek, with a palpable nodule of the malar eminence. On the right leg, left arm, right shoulder and biceps areas, and right buttock there is a macular eruption. Papules and nodules, 0.5 to 8 mm., are numerous on the extremities. On the left nostril there are superficial ulcerations. The left ulnar nerve is readily palpable and tender, and pressure on it results in paresthesia. The right great auricular nerve is also palpably enlarged. There is weakness of the left hand, with atrophy of the left first dorsal interossei. Pin-prick anesthesia is present on the left hand and forearm but not on the thumb, and hypalgesia, on both calves.

Scrapings from the nasal ulcerations contain many acid-fast bacilli. The patient just arrived in this area, and a biopsy performed only a few days ago, from which the slides were made, shows the picture of lepromatous leprosy, with many acid-fast bacilli.

Discussion

DR. PAUL FASAL: Clinically and histologically this is typical lepromatous leprosy and presents many fascinating problems. The patient needs treatment and should have some reasonable form of isolation. He should not remain in the service.

He could be treated as an outpatient, provided there is no contact with small children. This must be insisted upon. In California we are treating an increasing number of outpatients with lepromatous leprosy, and generally they cooperate well. Unfortunately, one of these patients recently failed to keep his promise and visited his home and small children, and we had to send him to Carville, La.

There is no time limit in the treatment of lepromatous leprosy. The disease may need to be treated for the lifetime of the patient. They should not be discharged routinely after three years. As yet we do not have adequate drugs for lepromatous leprosy. Tuberculoid leprosy is different. The prognosis in this case is not bad, provided he continues regular and uninterrupted treatment. This must be prolonged. Contacts must be closely supervised, but prophylactic treatment of contacts is not advisable.

Lichen Sclerosus et Atrophicus. Presented by Dr. William M. George.

This 62-year-old man was presented before the society on Feb. 8, 1957, with an extensive thick-walled bulla over the right flank. Various medications, including prednisolone by mouth, effected only temporary improvement. Adopting Dr. Rolf Miller's suggestion for therapy (Lichen Sclerosus et Atrophicus, A. M. A. Arch. Dermat. 76:43 [July] 1957), the bullous lesion was removed in August, 1957, by dermabrasion with the rotating wire-brush technique. The 10×20 cm. area healed slowly and after six months shows mottled erythema and slight scaling and atrophy. A biopsy, performed on Feb. 10, 1958, reveals no recognizable lichen sclerosus et atrophicus.

A second feature of importance in this patient is the development of carcinoma in situ in an area of lichen sclerosus et atrophicus over the glans penis, sulcus, and foreskin. The degenerated area, measuring 1.7×1.2 cm., was surgically excised; circumcision was performed, and later a 1×1 cm. slow-healing area over the corona and sulcus was curetted and desiccated. Healing was uneventful and complete. The excised tissue shows lichen sclerosus et atrophicus, with areas of carcinoma in situ.

Discussion

Dr. Edward J. Ringrose: There has been considerable argument about whether lichen sclerosus et atrophicus on the penis (balanitis xerotica obliterans) becomes malignant. There is no doubt in this case that squamous cell carcinoma in situ has developed from this disease, particularly when the sections are examined.

Dr. William E. George: The urologist was determined to do a partial amputation on this man, and I was determined not to let him do it. I feel that carcinoma in situ in this location is curable by curettage and electrodesiccation. The patient is happy with the result.

Extensive Epithelial Nevus. Presented by Dr. Rolfe W. Salin.

Pigmented Nevus on the Nipple. Presented by Capt. D. G. Moyer (MC), A. U. S. (by invitation).

Perifolliculitis Capitis Abscedens et Suffodiens. Presented by Capt. Donald G. Moyer (MC), A. U. S. (by invitation).

Lentigo Maligna. Presented by Dr. Rolfe W. Salin.

Pemphigus Erythematoides. Presented by Dr. William M. George.

A Case for Diagnosis: Papular Urticaria? Presented by Dr. Manuel F. Allende and Dr. Thurid Lininger (by invitation).

A Case for Diagnosis: Linear Psoriasis? Presented by Dr. Edward J. Ringrose.

Pseudoxanthoma Elasticum. Presented by Dr. Eugene M. Farber and Dr. Roderick D. Sage (by invitation).

SAN FRANCISCO DERMATOLOGICAL SOCIETY

March 21, 1958

A Case for Diagnosis: Weber-Christian Disease? Presented by Dr. S. William Levy and Dr. John Wheeless (by invitation).

A 35-year-old woman first noted a small subcutaneous nodule on the left upper arm about one and one-half years ago. The nodule became larger, firm, tender, raised, and covered by slightly erythematous skin. Many similar lesions have since occurred on the extremities, abdomen, and buttocks. The lesions vary from 2 to 6 cm. in size. Some of the nodules rupture and exude a thick, yellow, oily substance and heal with a scar. Others absorb without scarring. Each nodule lasts from a few days to several weeks. A moderate fever accompanies the development of new lesions. Some appear in sites after minimal trauma.

Treatment with oral corticosteroids and with novobiocin (Cathomycin) was without effect.

Extensive laboratory studies, including blood chemistry and cultures of the material from the nodules, are negative. Two biopsy specimens are presented but show little pathologic change.

Discussion

Dr. George T. Wilson: About a year ago, I presented an 8-year-old boy with this condition.

Cortisone, 75-100 mg. per day, was prescribed for him, and the dose was gradually reduced. The lesions decreased in severity and number after four to six weeks. He had no further trouble until today, when he is seen with a single lesion. There are reports of patients with this condition who have been followed for extended periods, and apparently in most cases it disappears spontaneously after four to five years. It usually occurs in the younger patients.

DR. S. WILLIAM LEVY: The panniculitides comprise a rare and interesting group of diseases in which the cause is obscure. We are forced to make the diagnosis of this case on clinical findings alone, as the biopsy specimen does not show any changes in the fat. When a punch biopsy is done, only the liquid fat is obtained under normal skin. I shall try to remove a lesion in toto.

Weber-Christian disease is not entirely innocuous. Some 14 deaths have been described in this condition, from staphylococcic septicemia, uremia, and, in one instance, a liver disorder. It occurs three times as often in females as in males, and more in the 30's or 40's. The condition has been explained as an allergy which manifests itself in the blood vessels or fat, but the explanations do not seem satisfactory. I do not feel that steroids are going to be the answer in this particular case. The cases reported in the literature that have been treated with steroids have relapsed when the drug has been discontinued.

A Case for Diagnosis: Epidermodysplasia Verruciformis with Gingival Lesions? Presented by DR. HERBERT L. JOSEPH.

Since 1945, a female clerk, aged 40, has had small verrucous papules on the gums. Similar lesions appeared on the face about three years later.

She had a thyroidectomy in 1952. Both parents had the same surname, a common name in Italy, but consanguinity is denied. The mother is diabetic.

In 1948, an oral surgeon removed some of the warty tissue from the gingiva. A general pathologist reported this as squamous-cell carcinoma, and a hospital tumor board agreed with this diagnosis. The patient was very disturbed when told she had a malignancy but refused surgery. The slide was subsequently reviewed by several other pathologists, who disagreed and described the tissue as benign epithelial hyperplasia.

Some of the larger verrucae on the face have been removed by other physicians by electrodesiccation. Several have since been treated with liquid nitrogen. Oral bismuth was stopped when the gums became tender and bled easily. A topical keratolytic is now being used on the facial lesions.

Numerous small skin-colored papules are seen on the nose, nasolabial folds, lips, and chin. They are pinhead size and smaller. (Several, up to 1.0 mm., have been removed.) Similar lesions, with a yellowish-pink color, stud the gingivae, mostly on the outer surfaces. There are more on the upper gingiva, but many are present on the lower.

A slide is presented from a lesion removed from the chin as well as from the original one from the gingiva.

Discussion

DR. EDWARD J. RINGROSE: I do not believe this patient has epidermodysplasia verruciformis, but I am not certain what it is. I have a case with similar skin lesions but without oral lesions. The facial lesions look like molluscum contagiosum. In the sections it appears as though a peg of epidermis is driven down into the skin three or four times the depth of the normal epidermis. Dr. Hamilton Montgomery saw my patient and the slides. He was of the opinion that it was some sort of nevoid disturbance. Dr. Herman Pinkus, after examining the sections, suggested the possibility of a poroma.

DR. ARNE E. INGELS: How would you explain the mouth lesions?

DR. HERBERT L. JOSEPH: I agree that this is a nevoid ectodermal defect of some kind, perhaps a variant of epidermodysplasia verruciformis. The lesions on the face vary in appearance from that of flat to that of filiform warts. The possibility of consanguinity points up the hereditary factor. Consanguinity occurs in epidermodysplasia verruciformis. This disease has been reported on the lip and urethra. The gingival lesions are most unusual, and I have never seen anything remotely resembling them. Pseudoepitheliomatous hyperplasia in the original tissue from the gingiva prompted the general pathologists to label this as squamous-cell carcinoma. Perhaps if a dermatologist had been on the tumor board, the anxiety and distress of this woman would have been avoided.

Localized Scleroderma of the Breast Resembling Carcinoma. Presented by DR. KEMP H. DOWDY.

A 33-year-old white woman was seen initially in January, 1953, with a firm, thickened area of skin over the lateral portion of the right breast as a small indurated papule. She complained of pain and tenderness. A biopsy, in 1953, was inconclusive. The lesion has progressed slowly, with increased This had started approximately one year previously thickening and pain on movement of the right arm.

Recent biopsy specimens are characteristic of scleroderma.

Discussion

DR. EUGENE M. FARBER: I believe this patient has circumscribed scleroderma or morphea.

DR. ARNE E. INGLES: I should like to suggest that this might be a xanthoma.

DR. KEMP H. DOWDY: This is definitely scleroderma and presents a problem to the patient. All of the recent biopsy specimens show the histological picture of scleroderma.

The first impression on examination of this patient is, of course, en cuirasse carcinoma of the breast. She has been seen by tumor boards and has been very distressed because of this possibility.

The area has progressed considerably during the last year and a half. She has gained weight, and the breasts have become rather pendulous, causing pain when she raises her arm. The pain has increased so that she has considered having the breast amputated for relief. When she loses about 20 lb. of weight the pain is less. She has been given hyaluronidase by iontophoresis and local injections of hydrocortisone, none of which has done any good.

DR. GRANT MORROW: I have heard of the use of relaxin in this disease. Apparently it is necessary to give it with estrogen. It is of doubtful value.

Lepromatous Hansen's Disease. Presented by DR. M. WEINREB (by invitation) and DR. PAUL FASAL.

A Case for Diagnosis: Sarcoid? Tuberculid? Presented by DR. GEORGE T. LENAHAN.

The New, Newer, and Newest

The practice that many specialty societies have of holding their meetings at the time of the annual American Medical Association convention, in or near the convention city, has created an undesirable and serious situation. Some groups meet a day or two before the A. M. A. convenes; the specialty sections of the A. M. A. are held on the last three days of the convention. For various reasons, many dermatologists are unable to attend both meetings, and because the specialty groups meet on the weekend they cut deeply into the attendance of the A. M. A. sections. The practice is parasitic, unwise, and ungrateful, for the A. M. A. is the parent organization that set the pattern for all medical societies. Certainly, without an A. M. A., these specialty organizations would not exist, and if the meetings of the specialty sections of the A. M. A. are not well attended, they will inevitably be discontinued. Our own Society of Investigative Dermatology is one of the guilty ones. Some months ago there was the hopeful rumor that representatives of the two societies were in conferences designed to remedy the situation. I understand now that the efforts have failed, even though the A. M. A. was willing to set aside its long-established restrictions against combined meetings. It is unfortunate, because we are a relatively small group as specialists go, though widely distributed, and it would be to the advantage of all of us to get together frequently. Certainly the excellence of the S. I. D. meetings would continue to attract a full and interested attendance, and, coupled with the A. M. A. sessions, the two programs could be coordinated and developed so as to stimulate every dermatologist, whatever his interest, and each society would retain its independence and identity. Attendance at such a convention would be a rewarding five-day experience.

In 1957, there were 220,000 signed medical articles published in 4,000 medical journals, more than 1,000 of them in North America.

The New York Academy of Sciences held a conference on hair growth and hair regeneration in January. Irwin I. Lubowe was the Conference Chairman, William Montagna, the Session Chairman. Among dermatologist-participants were Richard Winkelmann, Norman Orentreich, Eugene Van Scott, and Albert Kligman. Other speakers were from the fields of anatomy, biology, biochemistry, zoology, and wool textile research. Unfortunately, the notice of the meeting was received too late to be of benefit to some of our readers who might have attended. In plenty of time, however, comes the notice that:

The 13th International Congress on Occupational Health will be held in New York City, July 25, 1960. Anyone interested in participating should communicate with Dr. Irving R. Tabershaw, 375 Park Ave., New York. Since skin diseases make up such a large proportion of compensable diseases, there should be dermatologists interested in participating.

The Noah Worcester Society, which was launched last year, is apparently in orbit. A second meeting, to be held in Hollywood, Fla., April 7, under the guidance of Alfred Weiner, President, Dan Kindel, Vice-President, and Jerry Lavender, Secretary, will be addressed by Dan Ritchfield, Ashton Welsh, Jerry Lavender, Alfred Wiener, William Slinger, Robert Pittelkow, Lawrence Goldberg, Adolph Loveman, Coleman Mopper, Louis Safer, Leonard Markson, and Arthur Kern. A wide variety of subjects will be discussed, including the colorful one of "vulvitides," and a "cordial" invitation has been extended to all dermatologists.

Marion Sulzberger delivered the Lloyd W. Ketron Lecture Feb. 19, at The Johns Hopkins Hospital, Baltimore, on the subject, "Some New Findings Concerning the Biology of the Skin Surface."

Young In Heart—Arthur W. Stillians celebrated his 87th birthday, Dec. 24, 1958. A birthday party, complete with cake and candles, at which Sam Zakon delivered the birthday eulogy, was held at Olivet Presbyterian Church of Chicago. Dr. Stillians is in active practice, attends local medical meetings regularly, conducts an active service at a charity hospital, is to be seen at the library frequently, still lectures occasionally, and smiles constantly.

Less happy note—Poor Brigitte Bardot, the body beautiful, broods about her acne.

HR

Abstracts from Current Literature

Pleuropneumonia-like Microorganisms on Skin in Various Dermatoses. N. Melczer and P. Vásárhelyi, Arch. klin. u. exper. Dermat. 207:431-444, 1958.

In 200 patients with various dermatoses, skin scrapings, pus, lymph, and blister content were inoculated on protein-rich media. Bacteria belonging to the group of pleuropneumonia-like micro-organisms (PPLO) were found in 45% of the cases. It appeared that in 6% bacterial L-forms grew, but most probably they represented PPLO. In one case of balanitis out of 24 cases examined anaerobic G-strains as described by Ruiter and Wentholt could be cultivated. Formations resembling elementary bodies as found by Melczer in gangrenous changes of the skin and mucous membrane do not represent PPLO. PPLO occurring on the skin are most probably saprophytes without pathogenetic importance.

Hollander, Springfield, Mass.

Importance of Redox Potential for Physiology and Pathology of Skin. H. Langhof, Arch. klin. u. exper. Dermat. 207:445-458, 1958.

The importance of the redox potential in the management of psoriasis, chronic arsenical poisoning, chloracne, and melanodermatitis toxica (Hoffmann) is discussed.

Hollander, Springfield, Mass.

Histo- and Biochemistry of Epidermal Intercellular Space in Normal and Pathologic Conditions. O. Braun-Falco and G. Weber, Arch. klin. u. exper. Dermat. 207:459-471, 1958.

Histochemical and biochemical studies were made on three specimens of normal skin, pemphigus with subepidermal blister formation, and epidermoid skin carcinoma. Hale-PAS-reactive material was found in the intercellular space of normal and pathologic epidermis. It is absent or present in minimal quantity between the cells of the basal-cell layer. This material probably represents an acid mucopolysaccharid originating from epithelium.

Hollander, Springfield, Mass.

Histologic and Bacterial Changes in Lepromatous Leprosy After Therapy with Diamino-Diphenil-Sulfon. St. G. Nicolau and P. Vulcan, Arch. klin. u. exper. Dermat. 207:486-498, 1958.

This is an account of examination of 120 patients with lepromatous leprosy. Distinct changes of lepra cells are found in the beginning of the second year of treatment. Resorption of the lepromatous infiltrate starts in the subcutis. Resorption of lepromatous tissue is usually complete after treatment of two and one-half to three years or longer of duration. Lepromatous changes of lymph nodes are slower than those of the skin. Already in the first months of treatment Hansen's bacilli diminish in numbers and change into a granular form. Finally they dissolve into a mass of fine fuchsinophil or cyanophil granulations. The authors could not determine if the final changes of the bacilli still represent live and reversible or definite degenerative forms. Hansen's bacilli in lymph nodes are more resistant to treatment than those in the skin. In four patients granular forms of bacilli were found after four and one-half years of therapy. The sterilization of the lymph nodes is the most important test of cure. There is discussion of periodic supervision of patients after discharge from the leprosarium.

Hollander, Springfield, Mass.

Systematized Circumscribed Scleroderma, Representing Predominantly Cervico-Thoracic Quadrant Syndrome. G. W. Korting and H. E. Korte, Arch. klin. u. exper. Dermat. 207:499-507, 1958.

A 63-year-old farmer showed circumscribed scleroderma, predominantly of the right shoulder and right arm, and atrophy of the left side of the face. The distribution of the sclerodermatous changes is compatible with the cervicothoracic quadrant syndrome. X-ray examination revealed extensive osteochondritis of the cervical spine. Perivasal sympathetic influences and spinal directional impulses are considered pathogenetically.

Hollander, Springfield, Mass.

RARE FORM OF POIKILODERMA: LUPUS ERYTHEMATOSUS-LIKE SKIN CHANGES IN DWARFISM. G. W. KORTING and W. ADAM, Arch. klin. u. exper. Dermat. 207:508-520, 1958.

In a 37-year-old male dwarf, erythema, telangiectasia, and follicular hyperkeratosis of the nose, zygomatic regions of the face, and ears; erythrocyanosis and atrophy of the distal part of the forearms and the dorsa of the hands; systematized nevus flammeus of the right gluteal region and the flexor aspect of the right thigh and leg, and lichen pilaris of the lateral aspect of the extremities were observed. Histologic findings: follicular hyperkeratosis, lacunar telangiectasia without surrounding cellular infiltrates, colloidal degeneration of connective tissue, elastica degeneration, and abundant perivascular pigmentation in the upper cutis (PAS-positive lipopigment). Further study of lipopigment in primary poikiloderma is necessary in order to determine if qualitative differences could be important in various types of poikiloderma.

HOLLANDER, Springfield, Mass.

HYPERERGIC PANVASCULITIS OCCURRING AS MULTIPLE SYMMETRICAL GANGRENE OF SKIN AND BONE. A. MATRAS, Arch. klin. u. exper. Dermat. 207:521-540, 1958.

A boy suffered from his fifth to seventh year of life (after extractions of abscessed teeth) from fever, erythema multiforme-like eruptions, swellings of joints, and purpura. Finally, symmetrical gangrene of various areas of the body with mummifications and mutilation of all fingers developed. Porphyrin was positive in the urine. Examination of the mutilated phalangeal bones with the fluorescence microscope revealed porphyrin as distinct illumination of pink-red to blue-red color. Death was due to diffuse purulent peritonitis with necroses of the gastrointestinal tract. Histologic examination of the submucosa of the intestines, mesenteric lymph glands, liver, spleen, myocardium, thyroid, adrenals, and skin showed hyperergic arterial changes, with fibrinoid necrosis of the media and inflammatory reaction of the adventitia. Hyperergic panvasculitis on an infectious-toxic basis is assumed as pathogenic hypothesis.

HOLLANDER, Springfield, Mass.

MICROBIOLOGICAL LITERACY. R. E. BUCHANAN, Bact. Rev. 22:204-215 (Sept.) 1958.

In a critical, scholarly fashion the author emphasizes the difficulties many writers have with scientific terms derived from Latin and Greek. He gives many examples of problems with pleurals and particularly taxonomy of various organisms. After 11 pages of helpful but nonetheless pointed criticism, he hurls his final barb under the heading "References": "None is cited. Each reader is referred to his own lectures and publications for examples."

BLANK, Miami, Fla.

RUBBER AND ECZEMA—I. COMMUNICATION. E. SCHULTHEISS, Berufsdermatosen 6:49-70 (April) 1958.

A bibliography and review of eczema due to contact with rubber and materials used in the rubber industry is presented.

BULEY, Champaign, Ill.

CAUSES OF OCCUPATIONAL DERMATOSES IN 2,741 CASES. J. V. KLAUDER, Berufsdermatosen 6:78:87 (April) 1958.

The author surveys the causes that led to occupational dermatoses in 2,741 cases. Primary irritants represent the largest group (27.8%), followed by accidents or injuries (22.1%), allergens (15.9%), wet nature of work (15.2%), detergents (9.8%), mineral oil products and other substances (7.0%), and physical or biological toxic agents (2.2%).

BULEY, Champaign, Ill.

THE INFLUENCE OF COAL ON PYOCOCCAL INFECTIONS IN GUINEA PIGS. H. MIERZECKI and A. GLAJCAR, Berufsdermatosen 6:87-93 (April) 1958.

Coal powder of various brands and pyogenic cocci suspended in isotonic saline solution were injected subcutaneously into the dorsal skin of guinea pigs. Large infiltrates and ulcers resulted. Control tests with separate suspensions of coal dust and bacteria produced similar reactions. The authors conclude that coal dust did not stimulate the infection and that certain coals even had an inhibitory effect on the bacteria.

BULEY, Champaign, Ill.

A TEST SERIES OF SKIN PROTECTIVE OINTMENTS. E. HEGYI, Berufsdermatosen 6:111-124 (June) 1958.

Single random methods for testing the effect of protective ointments are inadequate. The author describes a series of model tests which assay the physical, chemical, and biological

qualities of the ointments. Summarily, these tests render a more realistic picture of the value of the product examined.

BULEY, Champaign, Ill.

THE INCIDENCE OF EPIDERMOPHYTIA INGUINALIS AMONG THE MINERS OF LOWER SILESIA: THE INFLUENCE OF VARIOUS TYPES OF COAL ON THE GROWTH OF THE KAUFMANN-WOLF FUNGUS. H. MIERZECKI and Z. WALICHIEWICZ, Berufsdermatosen 6:124-130 (June) 1958.

The morbidity rate of epidermophytosis among miners under ground is 21.3%, and above ground, 17.56%. The authors explain the approximately equal rate of infection by the fact that both groups of workers use the same washrooms. The incidence of infections increases, however, with the higher humidity in the galleries, while the wearing of rubber boots seems to be of no etiological significance. Coal dust added to the media showed neither an inhibiting nor a stimulating effect on the cultural growth of the fungus.

BULEY, Champaign, Ill.

TETRAMETHYL-THIORAMDISULFID, A DERIVATIVE OF THIOUREATE AS A CAUSE OF ECZEMA AMONG LONGSHOREMEN. K. H. SCHULZ and W. P. HERRMANN, Berufsdermatosen 6:130-136 (June) 1958.

Five longshoremen, employed in unloading bananas, developed acute contact dermatitis. Patch testing revealed that these men were sensitive to the preservative, Tetramethylthioramdisulfid, with which the banana bunches were sprayed.

BULEY, Champaign, Ill.

WEBER-CHRISTIAN DISEASE WITH VISCERAL INVOLVEMENT. S. ORAM and G. COCHRANE, Brit. M. J. 2:281 (August 2) 1958.

A case is described of Weber-Christian disease in which there were systemic changes in addition to subcutaneous nodules. Fever with hepatomegaly and anemia developed 11 weeks before the development of typical skin lesions. During that early period, it was not possible to make a diagnosis. Liver specimens showed fatty degeneration. The patient recovered and has remained well. The authors review other cases in which there were systemic changes. These occurred primarily in the liver, spleen, and bone marrow. They suggest that the syndrome is a hypersensitivity response occurring in the reticuloendothelial system, with its primary manifestations in the skin.

NORINS, Chicago

RHEUMATIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSIS (SLE). M. SILVER, S. BERKOWITZ, and O. STEINBROCKER, Bull. Hosp. Joint Dis. 18:140 (Oct.) 1957.

Analysis is made of patients giving a positive L. E. reaction in order to correlate this finding with the clinical manifestations of the disease. Of 211 patients in an arthritis clinic, 15 had positive L. E. preparations and 12 had clinical evidence of systemic L. E. There frequently is a discrepancy between the severity of rheumatic symptoms and the objective signs in SLE. Many of the abnormal laboratory findings in SLE are accounted for by the alteration in plasma proteins in SLE. Some of the reactions of the L. E. preparations may have been false-positives.

LEVIN, Delavan, Wis.

HEMANGIOPERICYTOMA OF THE PALM. M. SPINNER, Bull. Hosp. Joint Dis. 18:140 (Oct.) 1957.

A tumor mass in the palm, 2×2 cm., which had been enlarging for a year, was excised. Microscopic examination revealed a hemangiopericytoma, apparently arising near the bifurcation of a digital blood vessel. Grossly, the tumors are glistening, yellow-white, and firm, and microscopically, they reveal the typical pericyte of Stout and Murray. This tumor is distinguished from the glomus tumor by difference of color and lack of pain. There is an over-all rate of 12% malignancy in the hemangiopericytoma.

LEVIN, Delavan, Wis.

SUDDEN GRAYING OF THE HAIR AND PSYCHIC TRAUMA IN ALOPECIA AREATA. G. KLINGMÜLLER, Dermatologica 117:84-92 (Aug.) 1958.

Without any preceding psychic trauma, a man of 62 with mixed dark and gray hair showed an almost complete head of gray hair within three days. Superficial examination would have led to the conclusion that this was a case of sudden graying of the hair, as reported many times by others. Further study showed that the case was one of alopecia

areata. The loss of black hair was followed shortly by the loss of gray hair. Regrowth of the hair followed the usual pattern of gray hair in the formerly alopecic areas. The author discusses the problems involved in the question of sudden graying of the hair. His observation provides a natural explanation, in fact that a very acutely occurring alopecia areata causes the pigmented hairs to fall out very rapidly, while the white hairs remain longer and thus give the appearance of the hair becoming white.

MONASH, Miami, Fla.

SERUM PROTEINS IN SCLERODERMA. Z. ŠTÁVA, Dermatologica 117:147-153 (Sept.) 1958.

Electrophoretic study of serum proteins in patients with diffuse and others with circumscribed scleroderma shows a rise in the γ-globulin fraction at the expense of the albumins. This increase roughly parallels the progression of the disease.

MONASH, Miami, Fla.

THE EFFECT OF INFECTION WITH THE CALMETTE-GUÉRIN BACILLUS ON DINITROCHLORBENZOL CONTACT ECZEMA IN THE GUINEA PIG. J. R. FREY and P. WENK, Dermatologica 117:154-164 (Sept.) 1958.

Sensitization of guinea pig skin to dinitrochlorbenzene is potentiated by simultaneous intracutaneous inoculation of BCG vaccine if both antigens are given simultaneously and in the same skin area, so that they reach the same group of regional lymph nodes. If the antigens are applied to separate skin areas, so that each reaches a different lymph node group, potentiation is absent or minimal.

MONASH, Miami, Fla.

INVENOL IN THE THERAPY OF PSORIASIS: PRELIMINARY REPORT. E. NEUMANN, Dermatologica 117:172-178 (Sept.) 1958.

Invenol, an oral sulfonamide (chemical name not given) antidiabetic drug, when given in a dose of two to three tablets daily for two months, produced marked improvement in 16 of 19 patients. However, in only two patients did the lesions disappear completely. Recurrences occurred in most cases but improved again with repeated therapy. A few patients showed some side-effects, such as leukopenia. Evidently, considerable care must be used in the treatment with this type of drug in a disease like psoriasis, which is prone to recurrence.

MONASH, Miami, Fla.

BEHCET'S DISEASE. E. SCHULZE, German M. Month. 3:125 (April) 1958.

Recent research into the neural manifestations of Behcet's syndrome, recurrent oral and genital ulceration associated with iridocyclitis, has revealed a virus etiology of the disease. Material from the enucleated eyes of two patients was injected intracerebrally into mice and into the vitreous of rabbits. The mice developed encephalitis and the rabbits chorioretinitis and hypopyon. This same virus material gave strongly positive complement-fixation and neutralization reactions with the sera of patients with Behcet's syndrome but not with normal sera. The use of the term Behcet's disease rather than Behcet's syndrome is now justified.

LEVIN, Delavan, Wis.

CUTANEOUS CANCER OF EAR AND NOSE AS A DISEASE OF OCCUPATION AND CIVILIZED LIFE. W. KINDLER, Hautarzt 9:195-197 (May) 1958.

This is a report of six cases of cutaneous carcinoma of the ear and nose in which an occupational injury or persistent irritation of eyeglasses was incriminated as being possible causative.

BULEY, Champaign, Ill.

LIVER DAMAGE DUE TO ISONICOTINIC ACID-HYDRAZID IN THE TREATMENT OF CUTANEOUS TUBERCULOSIS. P. ZIERZ and O. H. PAETZOLD, Hautarzt 9:209-215 (May) 1958.

Among 120 patients treated with INH, transient insignificant side-effects were observed in 18.3% of the cases. An interruption of the treatment became necessary in only 3% of the cases.

Disturbed liver function, found in 55% of the patients, reverted to normal under treatment with INH. In 10% of the treated cases, a disturbed liver function could be directly attributed to the drug.

To prevent serious liver damage, a close surveillance of the liver function, combined with prophylactic treatment with glucose and lipotropic substances, is recommended.

BULEY, Champaign, Ill.

EXPERIMENTAL AND CLINICAL EVALUATION OF THE MODE OF ACTION OF ATEBRIN AND RESOCHIN IN CHRONIC ERYTHEMATOSUS. A. WISKEMANN and H. KOCH, Hautarzt 9:215-218 (May) 1958.

The authors have demonstrated experimentally an anti-inflammatory effect of Atebrin and Resochin administered internally. At the same time, they have determined the ultraviolet absorption curves of these chemicals, and by means of clinical studies have shown that they do not exert their therapeutic effect by means of any light-blocking properties.

BULEY, Champaign, Ill.

THE PATHOGENICITY OF MICROCOCCI FOUND ON THE SKIN. J. MEYER-ROHN, Hautarzt 9:218-220 (May) 1958.

In determining the pathogenic character of micrococci, the positive plasma-agglutination test and the demonstration of hyaluronidase, phosphatase, and fibrinolysin are valuable criteria.

BULEY, Champaign, Ill.

THE PLASMOCYTOMA AND ITS CUTANEOUS PATHOLOGY. A. LEINBROCK, Hautarzt 9:249-259 (June) 1958.

The internal symptomatology of plasmocytoma is presented in monographic form, and the specific and nonspecific cutaneous changes which may accompany the disease are discussed. Special consideration is given to the disturbance of blood coagulation and its pathogenesis. The findings in the author's own case of plasmocytoma are reported.

BULEY, Champaign, Ill.

LYMPHADENOSIS BENIGNA CUTIS AS A TRANSFERABLE INFECTIOUS DISEASE: III. COMMUNICATION. J. M. PASCHOUD, Hautarzt 9:263-269 (June) 1958.

In continuation of previous reports, two additional observations substantiate the concept that lymphadenosis benigna cutis may occur (1) in the form of a solitary tumor-like infiltrate and (2) as an experimentally produced superficial nodule located in an area of erythema migrans. The histological changes in the skin and the regional lymph nodes are discussed in detail.

BULEY, Champaign, Ill.

DISSEMINATED ERUPTIVE COLLAGENOSIS ASSOCIATED WITH METACHROMASIA. J. GAY PRIETO, P. RODRIQUEZ PÉREZ, and M. ÁLVAREZ CASCOS, Hautarzt 9:300-304 (July) 1958.

A case of collagen disease with a disseminated eruption of small nodules with multiple metachromatic foci in the cutis is reported. An increase of γ-globulin in the serum and histopathological changes in the renal glomeruli are concomitant findings in this case.

BULEY, Champaign, Ill.

ARE HYPERKERATOSIS FOLLICULARIS IN CUTEM PENETRANS AND ELASTOMA INTRAPAPILLARE PERFORANS VERRUCIFORME IDENTICAL DISEASES? Z. ZAMBAL, Hautarzt 9:304-311 (July) 1958.

Clinical and histological observations of a case lead the author to the conclusion that the entities described under the names of (1) hyperkeratosis follicularis et parafollicularis in cutem penetrans, (2) elastoma intrapapillare perforans verruciforme, and (3) keratosis follicularis serpiginosa are identical dermatoses, occurring in patients with cutis hyperelastica.

BULEY, Champaign, Ill.

LYMPHADENOSIS BENIGNA CUTIS AS A TRANSFERABLE INFECTIOUS DISEASE: IV. COMMUNICATION. J. M. PASCHOUD, Hautarzt 9:311-315 (July) 1958.

In summarizing his previously published observations, the author concludes that lymphadenosis benigna cutis and erythema chronicum migrans are variations of the same infectious disease. The infectious agent is probably a virus which seems to be sensitive to penicillin.

BULEY, Champaign, Ill.

THE EFFECT OF MONO- AND DISACCHARIDES ON THE O_2-CONSUMPTION OF MICROSPORUM GYPSEUM. G. POLEMANN, Hautarzt 9:318-320 (July) 1958.

The oxygen consumption of microsporum gypseum in liquid media containing various mono- and disaccharides is studied in the Warburg apparatus. The results are reported and illustrated by graphic charts.

BULEY, Champaign, Ill.

BALNEOTHERAPY AS A PART OF DERMATOLOGICAL THERAPY. K. HEKELE and O. LOFFERER, Hautarzt 9:320-322 (July) 1958.

Four case histories illustrate the value of balneotherapy in the treatment of decubital ulcers, pemphigus, psoriatic erythroderma, and extensive eczemas.

BULEY, Champaign, Ill.

CORTISONE IN THE TREATMENT OF REACTIONAL CONDITIONS IN TUBERCULOID LEPROSY. R. A. LEWIS, K. KYI KYI, and R. EDWARDS, Internat. J. Leprosy 25:213 (July-Sept.) 1957.

It has been suggested that corticotropin (ACTH) and cortisone be used in leprosy only in cases of drug sensitivity and for complications of the eye. In the reactional state of tuberculoid leprosy, cortisone and DDS (diaminodiphenyl sulfone) were used in about a dozen cases. In all but one, edema and erythema were controlled after 12 weeks of treatment and 4 gm. of cortisone. No exacerbation of neuritis and no untoward symptoms developed while patients were on this therapy, but the relatively high cost is emphasized.

LEVIN, Delavan, Wis.

STUDIES ON ENZYMES IN THE SKIN: THEIR USE AS A RESEARCH TOOL. R. D. GRIESEMER, J. Soc. Cosmetic Chemists 9:148-158 (May) 1958.

A short review of enzymology is presented, with specific reference to experimental assay of enzymes in the skin during the hair cycle of the rat. The rat's skin thickens during the first four days of the cycle. A similar phenomenon occurs upon exposure to detergents, and an enzymatic test is suggested for use in the evaluation of detergents.

BAIRSTOW, Chicago.

METHODS FOR REDUCING MELANIN PIGMENTATION OF THE SKIN. N. B. KANOF, J. Soc. Cosmetic Chemists 9:160-166 (May) 1958.

Monobenzyl ether of hydroquinone is the most effective agent in effecting depigmentation of the skin. Mercury compounds and ascorbic acid have limited value in this regard. Formed melanin can be removed from the skin by peeling agents—trichloracetic acid, ethyl chloride or Freon sprays, cryotherapy, and dermabrasion. Sunscreens can be used to prevent the formation of excess melanin but may still allow pigment darkening.

BAIRSTOW, Chicago.

THE LIPID ASSAY OF THE SKIN. H. E. WORNE, J. Soc. Cosmetic Chemists 9:181-187 (May) 1958.

Skin lipid assays were performed on 10 children and 18 adults. Previous work was confirmed that as one grows older the cholesterol in the skin decreases. Studies were also done on the amount of each unsaturated fatty acid found.

BAIRSTOW, Chicago.

SKIN AND HAIR PIGMENTATION. A. L. LORINCZ, J. Soc. Cosmetic Chemists 9:197-209 (May) 1958.

A lucid and excellent summary of the subject.

BAIRSTOW, Chicago.

FLUORESCENT PIGMENT OF MICROSPORUM. F. T. WOLF, E. A. JONES, and H. A. NATHAN, Nature, London 182:475-476 (Aug. 16) 1958.

The authors present additional infrared spectroscopic data, as well as microbiologic assay, to substantiate their earlier work that the fluorescent pigments of Microsporum canis and Microsporum gypseum are pteridines. Additional chemical observations are included, further describing the fluorescent materials.

BLANK, Miami, Fla.

EXPERIMENTAL RINGWORM IN GUINEA PIGS: ORAL TREATMENT WITH GRISEOFULVIN. J. C. GENTLES, Nature, London 182:476-477 (Aug. 16) 1958.

Griseofulvin is an antibiotic prepared from penicillium that is fungistatic in vitro and has been shown in plants to have systemic antifungal activity. The author administered it orally to guinea pigs experimentally infected with Microsporum canis 10 days after inoculation. At a dose of 60 mg. per kilogram a beneficial effect was noted clinically within four days. The author indicates that the drug is also effective when given orally to guinea pigs

infected with Trichophyton mentagrophytes and has been used successfully for the treatment of Trichophyton verrucosum ringworm in cattle. It seems to be of low toxicity.

BLANK, Miami, Fla.

RELEASE OF HISTAMINE FROM MAST CELLS BY TISSUE EXTRACTS. G. T. ARCHER, Nature, London 182:726-727 (Sept. 13) 1958.

Saline extracts of spleen, kidney, liver, and lung tissue from the rat and the rabbit and extracts of pigeon red cells, but not human red cells, release histamine when brought into contact with mast cells from the rat. The active histamine-releasing principle in splenic extract is probably a long-chain polypeptide containing arginine. The same histamine-producing substance was formed when human white cells were mixed with fresh antihuman white cell serum prepared in rabbits.

S. MONASH, Miami, Fla.

PASSAGE OF BACTERIOPHAGE PARTICLES THROUGH INTACT SKIN OF MICE. R. KELLER, Science 128:718-719 (Sept. 26) 1958.

By using a bacterial virus which does not multiply in an animal host but is readily detected in the laboratory, the authors demonstrated that the bacteriophage would pass through intact skin of the abdomen or the tail of a mouse. It was found in surprising quantity in the blood stream after the application to intact skin. As a result of this and previous work, the authors suggest a reinvestigation of the possibility that virus infections may occur by penetrations through the intact skin and of the effects this rather exotic mode of transmission may have in the epidemiology and pathogenicity of virus infections of man.

BLANK, Miami, Fla.

Books

Infectious Diseases of Children. By Saul Krugman, M.D., and Robert Ward, M.D. Price, $10. Pp. 340, with 44 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1959.

The majority of infectious diseases occur in childhood. This book, therefore, is intended to provide a concise account of such diseases. It is written primarily for pediatricians and general practitioners in whose practices most of these diseases are seen.

The greater part of the book is devoted to systemic infections, such as encephalitis, meningitis, hepatitis, Rickettsial infection, etc., yet there is much in the book to interest dermatologists. Consideration is given to the effect of these diseases when they occur in adults, as well as to infections such as pyoderms, exanthems, and herpetic diseases. There is even a chapter on control of communicable diseases in the hospital and at home.

The format is of the usual textbook type; the writing is plain, with an economy of words and emphasis on the practical; full use is made of diagnostic tables and illustrations, some in natural color, to recommend further the book, and of most importance is that the material is thoroughly up to date.

It is a good book to have at hand.

The Biology of Hair Growth. Edited by William Montagna and Richard A. Ellis. Price, $15. Pp. 520. Academic Press, Inc., 111 5th Ave., New York 3, 1958.

This reviewer is quick to confess to being favorably disposed toward any book that is dedicated to Stephen Rothman, "whose wisdom, kindliness and personal warmth are a constant source of courage and inspiration to all those doing research on skin." A reading of the book was most rewarding.

It consists of the papers read at the conference on the biology of hair growth held in London in 1957. Consisting of 21 well-written chapters by 23 distinguished international authorities, the papers provide information ranging from embryology and anatomy through the chemistry of keratinization, the nature of hair pigment, and aging of the human scalp, all thoroughly documented.

The material reflects especially the newer knowledge learned through modern laboratory methods of histochemistry, electron microscopy, etc. and clinical and animal research. A considerable part of the book concerns vascular patterns in animal skin and silkworm cells, wool production, and other information based on animal experimentation.

As is mentioned in the introduction by Rothman: "The pilary system is a perfect microcosmic structure. In the microcosomes we find birth, development, ageing and death, activity and rest, color formation and decolorification, greasiness and dryness, infection and sterilization. . . ." The various chapters deal with all of these, and though the emphasis is on the normal, with no discussion given to hair or scalp diseases, nevertheless, as Montagna points out in an excellent summarizing chapter, "these are the beginnings of our understanding of the morphological changes that occur in baldness."

The avowed purpose of the book is to serve as a source reference for all those interested in research on hair and hair growth, and this it does admirably: There are numerous illustrations in black and white; each chapter furnishes pertinent references, and the book is well indexed. Though the material is rather technical, it is throughout very readable and merits high recommendation.

Coccidioidomycosis. By Marshall J. Fiese, M.D., F.A.C.P. Price, $9.50. Pp. 186. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

In the minds of altogether too many practitioners of medicine, coccidioidomycosis is still considered to be a very rare, chronic, highly fatal, granulomatous infection worthy of study only by those who of necessity may very occasionally be brought into contact with such patients because of their practices being located in certain endemic geographic areas. The fact is that it is newly acquired each year by persons numbering in the thousands, among whom are many who are only in transit through the endemic region, or who otherwise soon

leave it to travel elsewhere. There is ample time between exposure and the onset of clinical symptoms for any spot on the globe to be reached. If given proper care, almost all of these patients will recover completely; if not, some will die unnecessarily and under appropriate circumstances might cause new endemic foci. The diagnosis is usually not difficult, and all doctors should be prepared to make it.

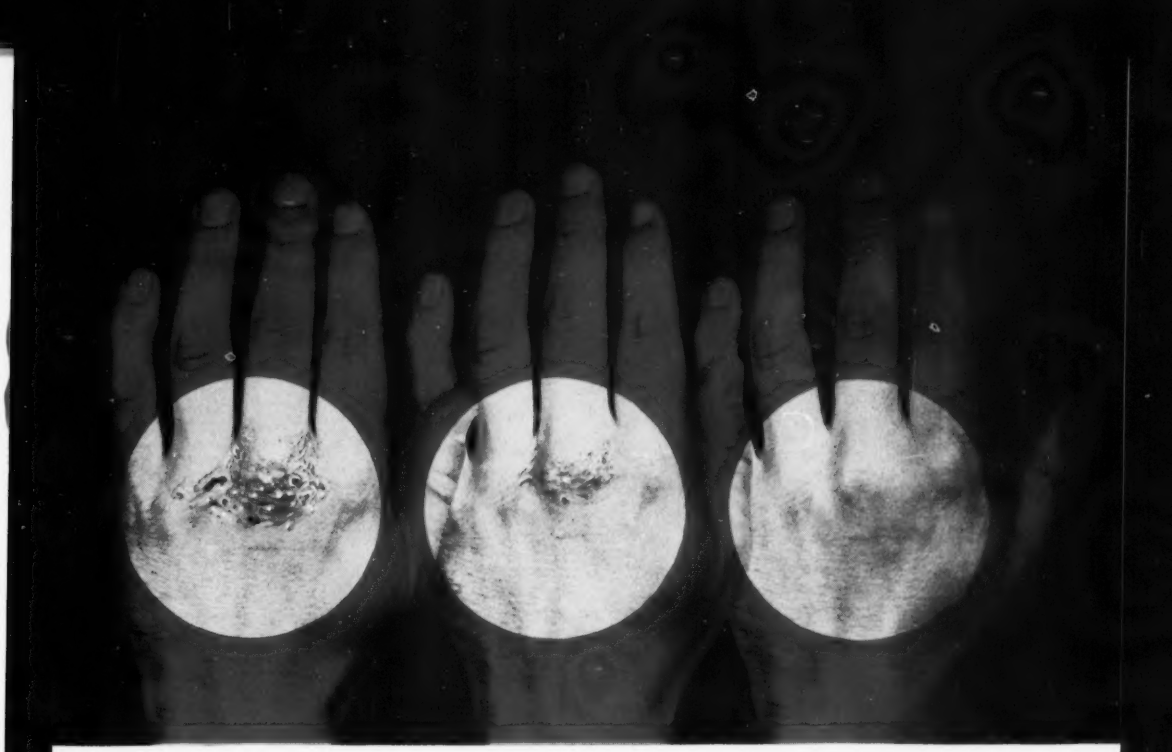
In addition, facts learned from studying coccidioidomycosis have already served to clarify some aspects of the immunology and epidemiology of other more common infectious diseases, and more such clues seem reasonably to be anticipated.

Dr. Fiese has written the first really complete monograph on this disease, and yet it contains only 186 pages. The interesting history is briefly covered; the mycology, epidemiology, immunology, and pathology are admirably detailed; the clinical syndromes are clearly described, and the treatment, discussed adequately. A complete bibliography—cross indexed by title, author, and chronology—is appended. This book will prove worth reading and subsequently worthy of a place on most quick-reference shelves.

Ocular Allergy. Frederick H. Theodore, M.D., F.A.C.S., and Abraham Schlossman, M.D., with chapters by William B. Sherman, M.D., and Robert S. Coles, M.D. Price, $12. Pp. 420. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This is a comprehensive work, covering the field in an up-to-date, practical manner. Ocular hypersensitive reactions, for example, are divided into anaphylactic, atopic, microbial, and contact reactions as they affect the various anatomic sites—conjunctiva, eyelids, cornea, sclera, uvea, etc. Contact reactions, as from eyedrops and cosmetics, are discussed in great detail and with a sureness that reflects experience. In fact, more detailed consideration is given to the role of cosmetics than appears in some dermatologic textbooks.

The writing is clear, and the book abounds with illustrations, but too few are in natural color, and there is an extensive bibliography. The material is current and reflects accurately modern concepts of the complicated subject.



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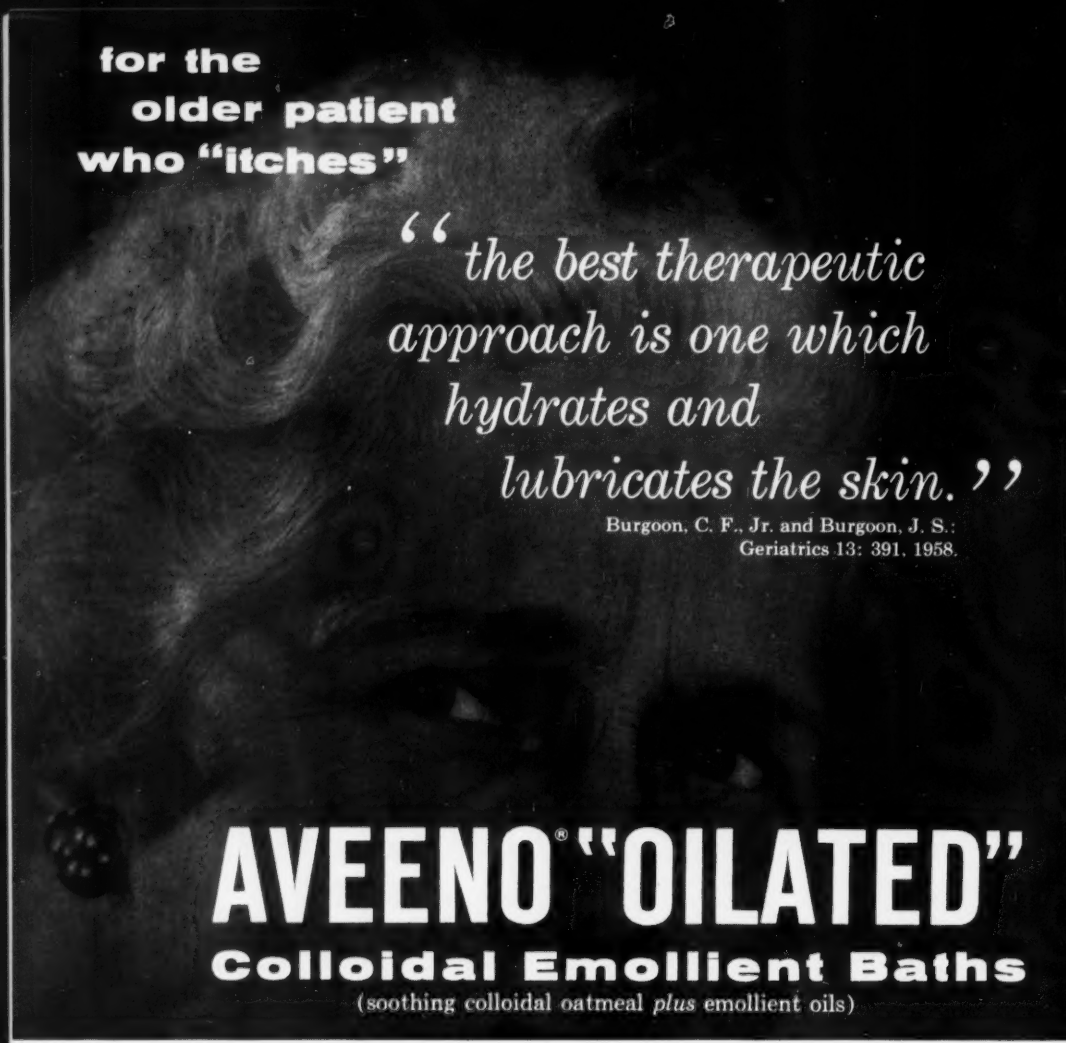
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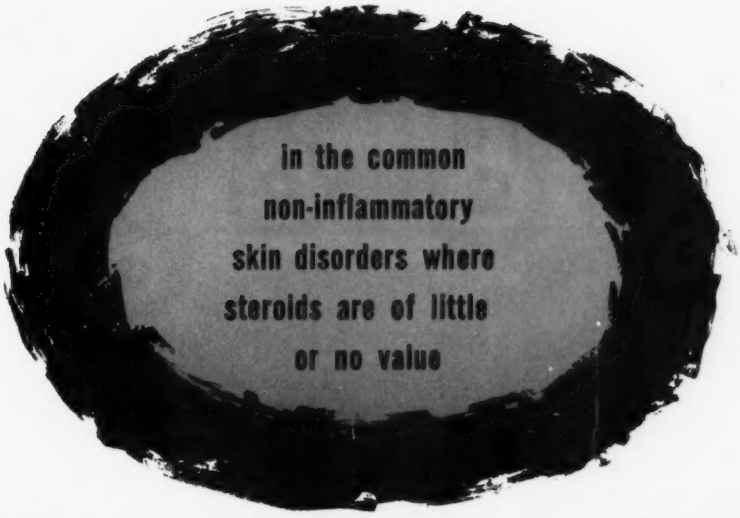

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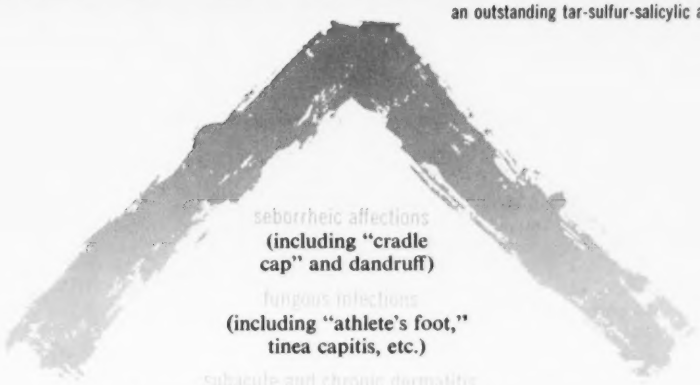

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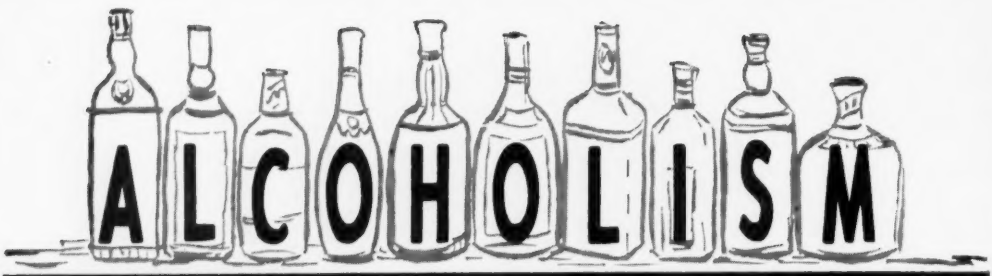

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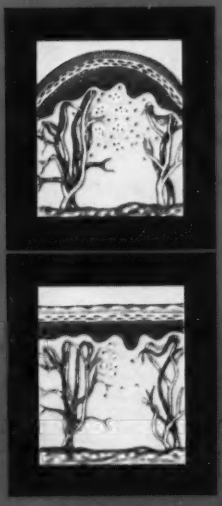

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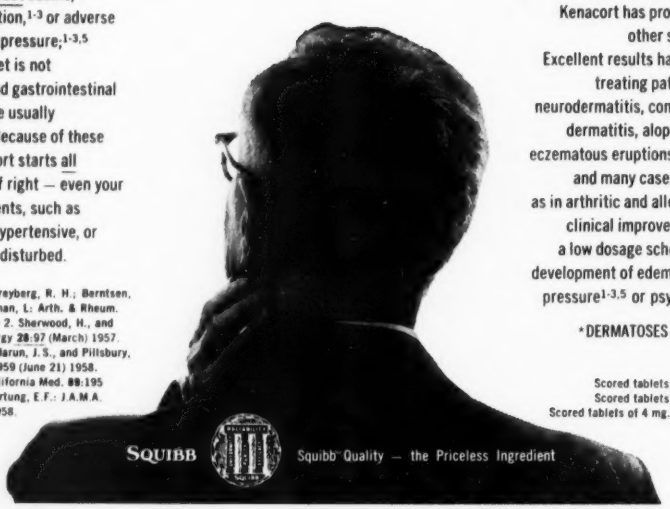
REFERENCES: • 1. Freyberg, R. H.; Berntsen, C. A., Jr., and Heilman, L: Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.



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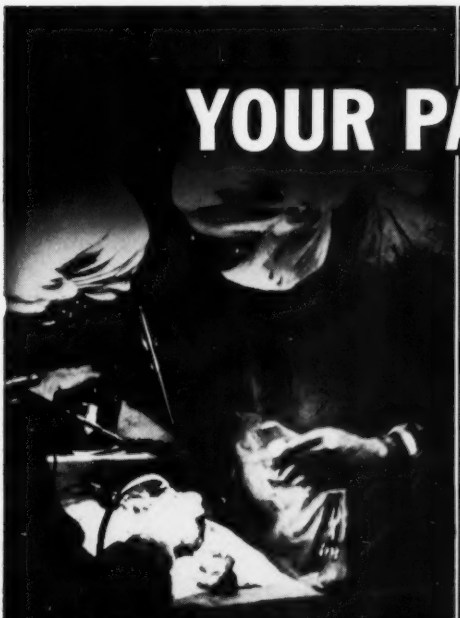

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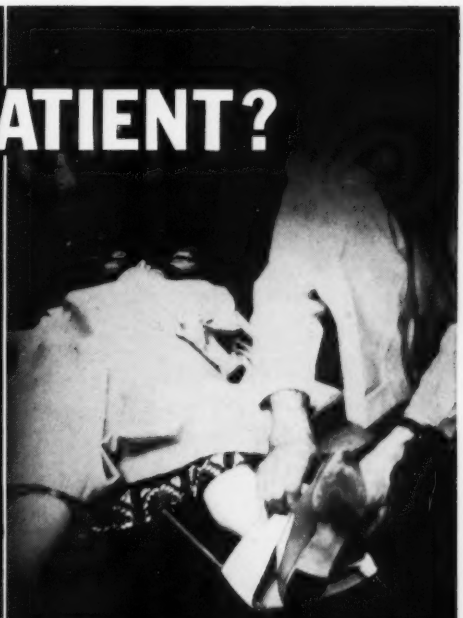

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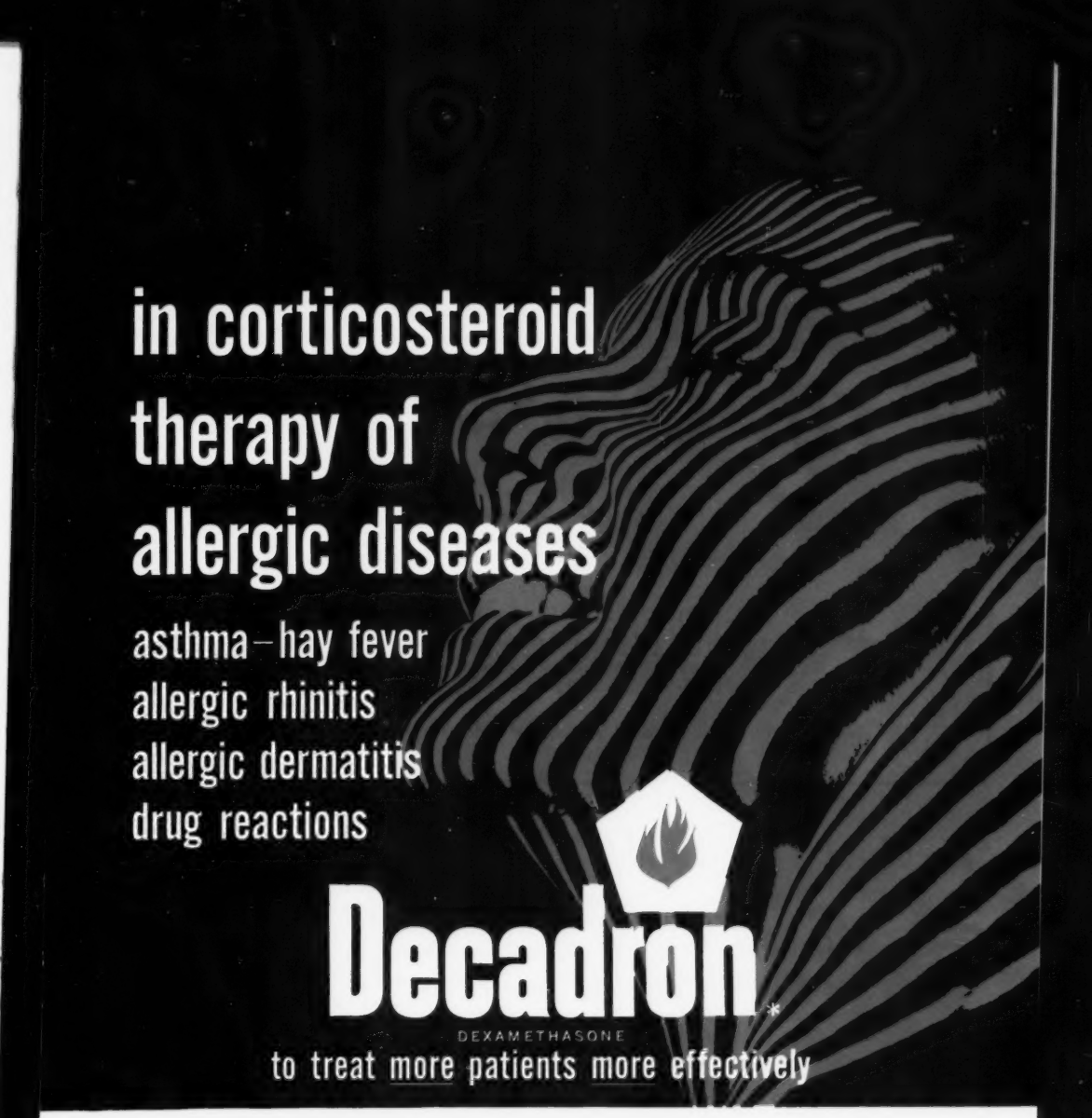

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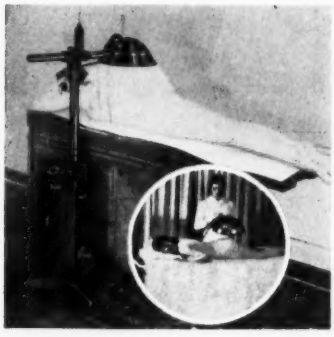

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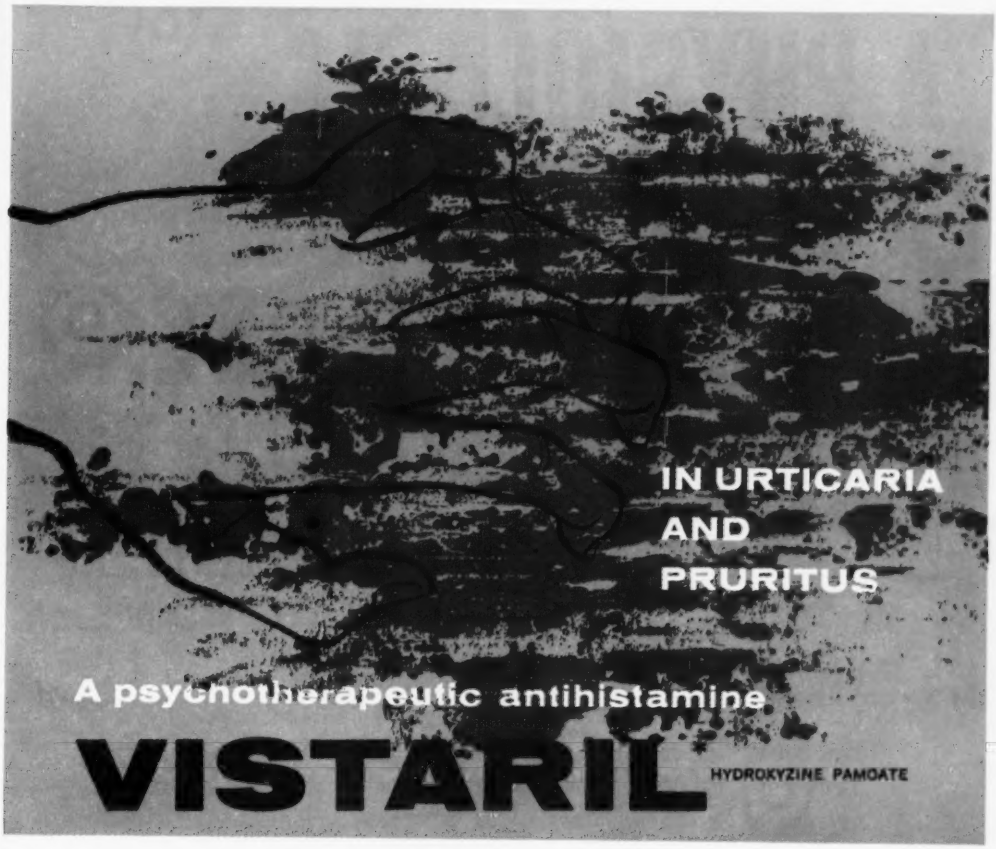

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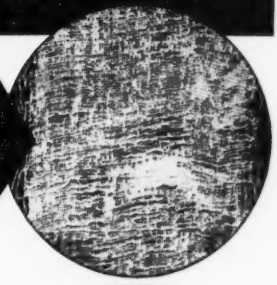

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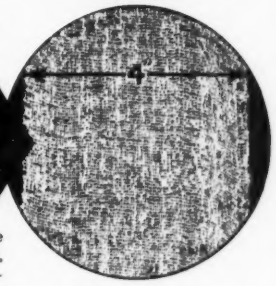

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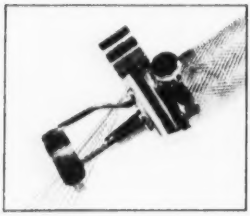

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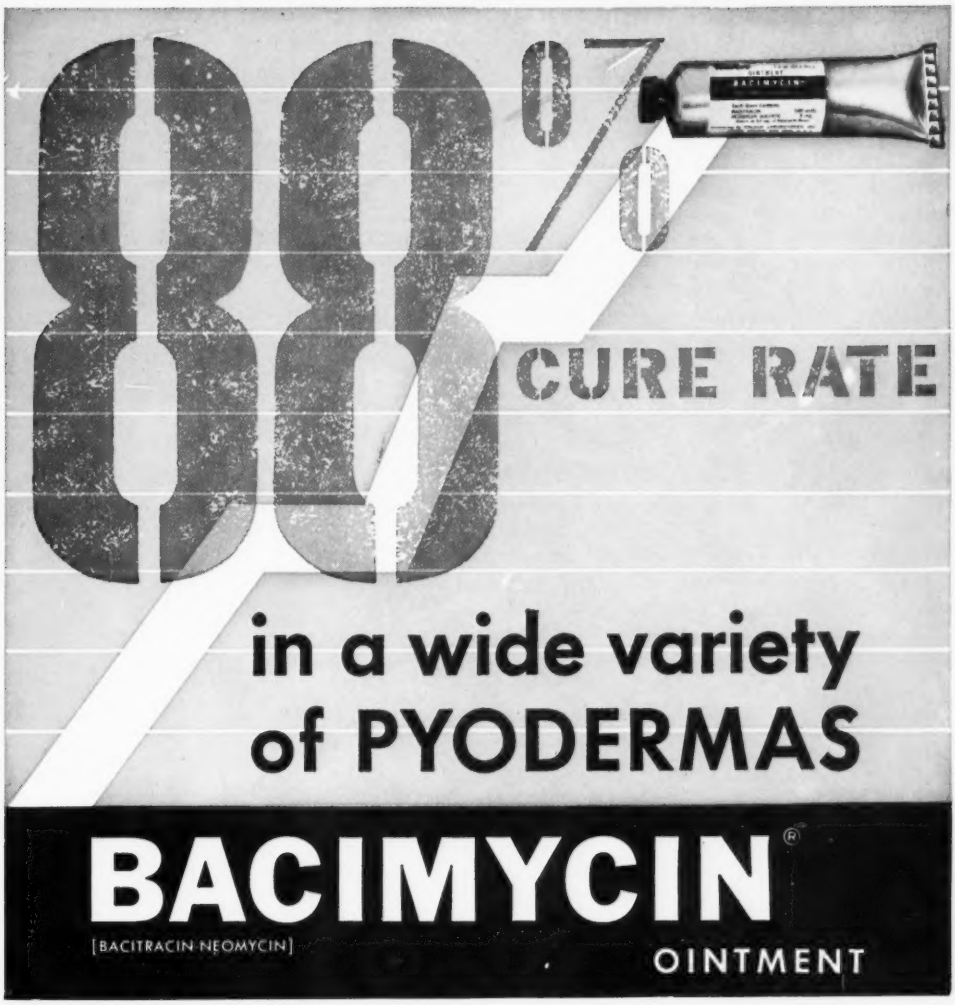

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1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

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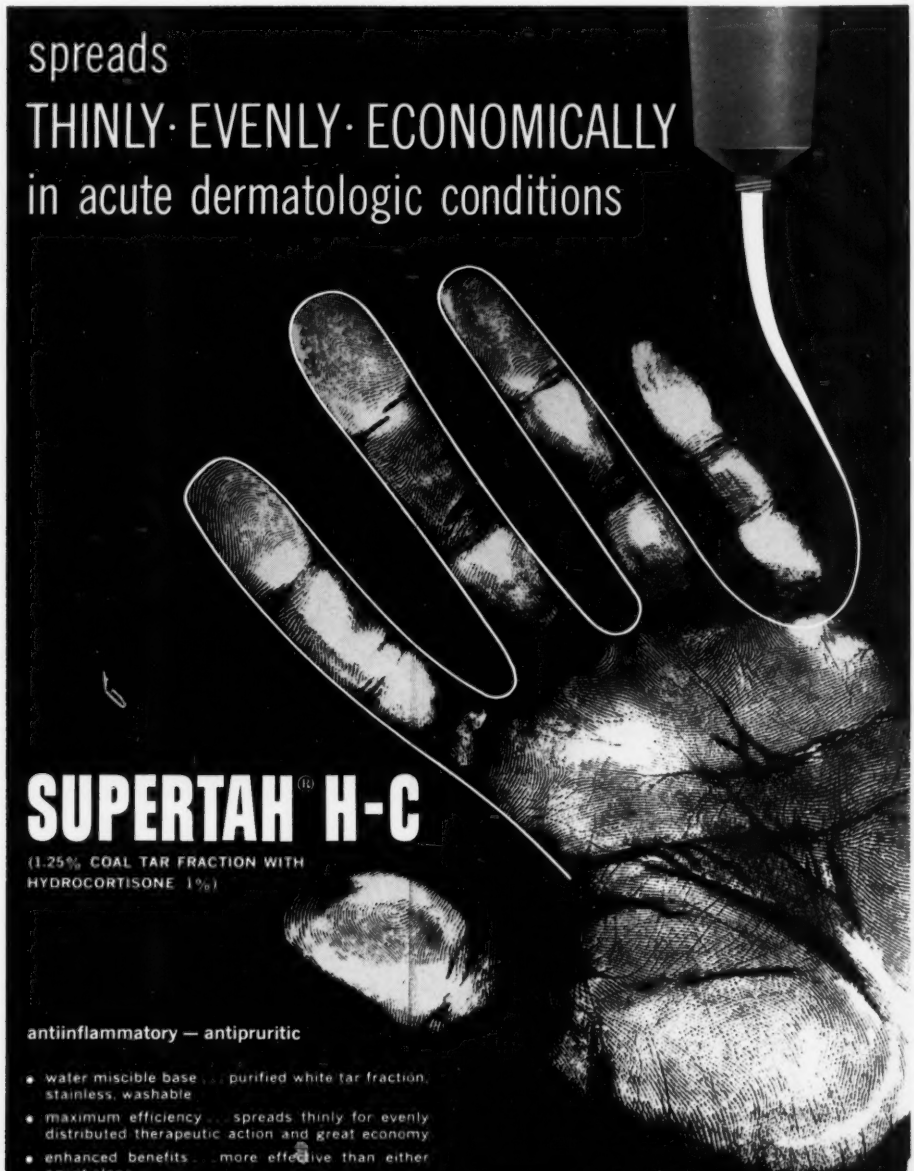

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